

Johns Hopkins University

**A MANUAL FOR APPLYING TO THE NIH COLLABORATIVE UG3/UH3
CLINICAL TRIAL ANNOUNCEMENT: PAR-18-407**

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Abstract

Academicians dedicate a significant part of their career to conducting research and publishing their findings. A major milestone in an academician's career involves being successfully funded to conduct research work. One measure of success in conducting medical research is the ability to obtain federal funding through the U.S. Department of Health and Human Services, National Institutes of Health (NIH) and its related Institutes, by submitting an extensive and competitive application for the agency's scientific review. The application process is arduous and requires the development of scientific and administrative components for submission within tight timelines, and it can take more than one attempt to submit a successful proposal resulting in funding. The submission process for each application can take up to eight months of preparation as its development requires dedication, patience, and passion. Researchers, who attempt the federal funding application process, speak to the need for their predecessors to provide support and directions systematically, to help them understand the funding opportunity announcement, application requirements, and plan for success.

This project involves the construction of a manual to assist researchers with submitting an NHLBI grant application using the funding opportunity announcement PAR-18-407 for multi-site clinical trials. The manual provides a step by step approach to completing the application sections using this FOA, the SF424 form and the author's own experience in submitting a grant to this announcement over three years. Instructions for each section of the application including sample templates are included in the manual to guide the PI with the successful planning and development of a robust application, effective use of time and establishing collaborations. The manual will help complete an

entire PAR-18-407 application successfully to obtain a favorable review outcome which translates into a funded research project.

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Glossary

Funding Opportunity Announcement (FOA): Advertisements announcing the availability of funds to support research, released by funding agencies such as the NIH

Grantsmanship: The skill of applying for grants and obtaining funding successfully.

Program Announcement special receipt/referral or review (PAR): Announcements related to areas of increased priority or funding mechanisms for a specific area of science. These announcements are usually valid for 3 years from the date of release unless otherwise noted.

Sponsored Programs Administration (SPA): A department within a university that works with researchers in administering sponsored projects such as federal research grants or industry funded research and offers pre and post award services such as grant application and budget development, administration of an awarded project and ensuring compliance with research regulations.

List of Abbreviations

DHHS	Department of Health and Human Services
EC	Executive Committee
eRA	electronic Research Administration
FDA	Food and Drug Administration
FOA	Funding Opportunity Announcement
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
NEH	National Endowment for the Humanities
NIH	National Institutes of Health
NHLBI	National Heart, Lung and Blood Institute
NSF	National Science Foundation
PAR	Program Announcement Receipt
PI	Principal Investigator
R&R	Research & Related
SF	Standard Form
SPA	Sponsored Programs Administration

Chapter 1. Introduction

1.1. Background

The National Institutes of Health (NIH) is a federal agency created to support medical and health-related research on an international scale. As a division of the U.S Department of Health and Human Services (DHHS), the NIH is synonymous with funding projects which have contributed to large scale medical breakthroughs both in clinical practice and in basic scientific research. The NIH is commonly referred to as the agency and had its humble beginnings in 1887 as a single-room laboratory commissioned to study the existence of bacteria and its role in infectious diseases as discovered by scientists in Europe.¹

Through subsequent years of growth to meet the needs of discovery in healthcare, coupled with the availability of federal funding and with Congress' involvement, the agency was formally recognized as the National Institutes of Health in 1930. The agency branched out into several divisions as funding became available. Each division caters to a specific field of medicine in the pursuit of a more focused pathway of research into disease and health. Currently, the NIH is made up of 27 divisions called Institutes or Centers.² While twenty-four of these Institutes receive federal funding and develop and manage their own budgets, all institutes and centers work under the Office of the Director and are required to follow DHHS policies and to develop research programs and funding opportunities.

¹ "A Short History of The National Institutes of Health" National Institutes of Health, accessed February 2019, <https://history.nih.gov/exhibits/history/index.html>

² "Who We Are/Organization," National Institutes of Health accessed February 2019, <https://www.nih.gov/about-nih/who-we-are/organization>

One of the institutes of the agency is the National Heart, Lung and Blood Institute (NHLBI) which oversees cardiovascular, respiratory, blood and sleep disorder research. Of the units within the NHLBI, the Division of Cardiovascular Sciences is of particular interest to the author of this paper, as it supports the study of cardiac and vascular diseases which rank as the leading cause of deaths in the world. Research in this area is continually evolving, and the NHLBI provides several opportunities for scientists to apply for federal funding and support their research ideas.³

1.2. Statement of the Problem

Each of the NIH Institutes solicits proposals for research funding several times a year based on the agency's funding cycle. Researchers all over the world are beneficiaries of this funding and vie for limited dollars to help advance their scientific work. Each of the NIH Institutes release Funding Opportunity Announcements (FOA) seeking proposals for review through their pre-defined and transparent peer review process. This peer review process includes a Scientific Review Committee appointed to review and score proposals received for funding consideration. Researchers that apply to the agency for funding can range from postgraduate students to early-careerists, to highly experienced scientists. The agency categorizes funding pools and announcements to seek proposals from a specific group of applicants (e.g., early careerists, postdoctoral fellows) to promote fair competition and encourage all levels of research ideas to compete for

³ "Division of Cardiovascular Sciences," National Heart Lung and Blood Institute, accessed February 2019, <https://www.nhlbi.nih.gov/about/divisions/division-cardiovascular-sciences>

financial support. The NIH also uses the standardized form (SF) 424 to ensure that relevant and consistent information is submitted for review. The FOA requirements dictate which sections of the SF424 form need to be completed. Applicant institutions and Principal Investigators (PI) must submit their proposal using the appropriate SF424 application and federal grants websites such as www.grants.gov.

Completing the SF424 and constructing a full application can be a challenging task for not only the new or first-time applicant but also a seasoned researcher. The Sponsored Programs Office (SPA) at the applicant university can assist with the SF424 completion; however a majority of the information required for submission has to be provided by the PI's research team, and this adds to the challenge.

The Principle Investigator's (PI's) team is expected to write the entire proposal which includes the scientific components, project budget and other administrative information required to execute the project successfully. Following the FOA and SF424 instructions are perceived to be a daunting and stressful task as there is very little room for error. The NIH provides several tools to assist with grant writing and approaching the application process, but it takes dedication and continuity in following all the requirements and submitting a complete proposal which is acceptable for review.

1.3. Project Question

Successful grantsmanship is an art developed over time. It can take several months to write a full proposal that meets the standards for submission and is considered review worthy. The PI may begin working on pilot data, building a research team and

establishing meaningful collaborations years before the application process is initiated.⁴

When working on an NIH application, the PI must decide how much information to include on the submission. With page limits and the specific information requested by the FOA on different sections of the application, the PI must construct a complete, succinct and impactful submission which is distinct and stronger than competing proposals.

Guidance available for the PI may be located on the internet and through the NIH. It can range from being generic to extensive, and it is up to the PI to determine which source is most helpful in providing an accurate and complete roadmap towards successful funding.

The need to share this author's experience of learning the grant submission process from basics, along with tips and feedback received over three years of the submission process on the NHLBI FOA PAR-18-407 has resulted in this project being undertaken to provide a practical manual covering the grant submission process. Several elements of the manual are common to various NIH grant submission announcements since the agency uses the generic SF424 form. However, this manual is best suited to complete the scientific and administrative sections of the PAR-18-407 announcement released by the NHLBI. The manual includes instructions and tips obtained while applying to the NHLBI Division of Cardiovascular Sciences under this FOA, involving human subjects' research in a clinical trial setting.

1.4. Project Objectives

The primary objective of this project is to generate a manual outlining the approach to a specific NHLBI FOA: PAR-18-407: Clinical Coordinating Center for

⁴ Karina Berg et al. : Demystifying the NIH Grant Application Process," Journal of General Internal Medicine, 2007;22(11):1587-95, doi: [10.1007/s11606-007-0301-6](https://doi.org/10.1007/s11606-007-0301-6)

Multi-Site Investigator-Initiated Clinical Trials (Collaborative UG3/UH3 Clinical Trial Required).⁵ The approach to this involves dividing the application into smaller sections while systematically constructing the complete submission. The author uses this NHLBI announcement to help explain the different steps in application development. It is the author's objective to create a manual that will include:

- Instructions on writing the scientific components of the application such as the descriptive title of the project, project summary/abstract, project narrative, bibliography and references cited, specific aims, research strategy, and the statistical design and analysis. Instructions on completing the administrative sections of the application include the cover letter, facilities and resources, equipment, biosketch for senior key personnel, structure of the project team, recruitment of women and minorities, overall recruitment and retention plan, single IRB plan data and safety monitoring plan, letters of support required, data dissemination and resource sharing plan and study timelines. Additionally, the manual will discuss budget development and human subjects' protection as part of the clinical trial required for this FOA.
- Steps to remain organized when developing the application for submission, by identifying sections that can be developed in parallel and those needed to be done successively.
- Sample templates will be included in some sections as examples to assist the PI in application development.

⁵ Clinical Coordinating Center for Multi-Site Investigator Initiated Clinical Trials (Collaborative UG3/UH3 Clinical Trial Required): PAR 18-407," Department of Health and Human Services, posted date 26 October 2017, <https://grants.nih.gov/grants/guide/pa-files/par-18-407.html>

- Strategies for efficient utilization of available resources by assigning the development of sections of the application to the staff at the university, within the research team and those completed by the PI and collaborators.

1.5. Significance

The author of the project faced challenges and learned to develop and submit an NHLBI grant over three years. There have been instances where a detailed manual like the one developed from this project would have provided the author with adequate guidance and eliminated surprises during the proposal development and submission process. Additionally, the author's submission has been reviewed by the NHLBI Scientific Review Committee twice, thereby providing the author with the unique opportunity to include some of the feedback as useful tips for users of the manual during their initial submission.

The NHLBI does not restrict the number of applications it will accept for review under this announcement or fund in each cycle, but the chance of obtaining funding after high scoring applications are awarded, affect each applicant's success rate significantly. For example, the budget on a high scoring application may take away 60% of the NHLBI funding available in that review cycle or fiscal year and allow a few additional applications to be funded in the remaining 40% of available dollars. It takes 6-8 months for the PI to complete a large application successfully. These challenges underline the importance of submitting a proposal that meets all requirements and aligns with the NHLBI mission in order to obtain a fundable score in the first round itself. The author's experience completing this process at an accelerated pace within three months with

exposure to revising the submission based on reviewer feedback will assist applicants and give them a head start on creating a robust application by using the manual.

1.6. Exclusions and Limitations

Despite its attempts to be all inclusive, the manual does not assist with submitting applications to all types of funding announcements released by the NIH or NHLBI. The NIH's goal for each announcement is varied and targets a different audience of applicants and a range of topics. The application form or the SF424 includes a specific set of instructions and further branches out to cater to different categories of applications. Attempting to provide a manual to cover all types of announcements and navigating through the various SF424 formats is not within the scope of the author's experience or this project. Readers are encouraged to use the process described herein to investigate appropriate and applicable processes related to the announcement to which they are applying.

Chapter 2. Review of Literature

2.1. Overview of Literature Review

Information for developing the manual for this project included resources available from the National Institutes of Health and its various centers. There are several tips on the agency website including examples and videos available to the grant writer at no cost. Articles from course work, including interactions with students and Professors in the Master of Science in Research Administration Program at Johns Hopkins University, have also provided information in developing manual content. Finally, the author's own experiences through interactions with the NIH Program Officer, NHLBI staff consultation meeting, working with the applicant university grant administrators, project collaborators and revising scientific content developed by the Principal Investigator through the three-year application process have provided valuable material for inclusion in the manual.

2.2. Developing Manual Content

To obtain a broad understanding of the challenges of the application process and the various approaches shared by experienced applicants, the author reviewed different topics related to grant writing, funding and peer review as follows:

- The manual covers instructions for an announcement related to clinical trials, and it was essential to understand if there were discrepancies in the funding rates of clinical trials versus laboratory research applications. An article on

the application and review process of resource grants within the National Library of Medicine provided insights in this regard.⁶

- Several universities have dedicated websites and department pages with grant writing tips and institutional policies. The author reviewed the Sponsored Programs Office webpage at the University of California at Berkeley for information on budget development, and The University of Texas Southwestern Medical Center Sponsored Programs Administration home page for grant submission processes.^{7,8}
- As a research administrator, the author supported an application with an annual budget greater than \$500,000 in direct costs per year of funding for the chosen announcement. The NHLBI process for this budget category required an in-person staff consultation meeting with agency officials. Meeting experiences from the staff consultation in October 2015 along with guidance from the agency in this regard have been included in the manual where applicable.⁹

⁶ Virginia Massey Bowden, "National Library of Medicine resource grants: application and review," Bull Med Library Association 80(2), April 1992,

<https://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC225639&blobtype=pdf>

⁷ "Proposals and Awards," Berkeley Sponsored Projects, UC Berkeley, Accessed February 2019, <https://spo.berkeley.edu/proposal.html>

⁸ "Sponsored Programs Administration(SPA):, UT Southwestern Medical Center, Accessed February 2019, <https://www.utsouthwestern.edu/about-us/administrative-offices/sponsored-programs/>

⁹ "Applications with Direct Costs of \$500,000 or More in any One Year," National Institutes Of Heart, Lung and Blood Institute, revised February 9 2018, <https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/applications-with-direct-costs-of-500000-or-more-in-any-one-year>

2.3. Project Specific Literature Review

The literature reviewed in support of this project has provided content for the manual and has helped the author in organizing the information and simplifying its presentation and layout.

The author began this project by reviewing information related to grants and federal funding available on the National Institutes of Health website and assimilated relevant information into the manual. The NIH page on grant writing tip sheets has videos and information which provide an introduction to the grant writing process. It is highly recommended that new investigators review these pages on the website before they embark on the application process.¹⁰ The National Cancer Institute website includes tip sheets that cover grant preparation basics and steps to develop the application.¹¹ However, this information is available through several links and is not presented in a step by step manner, leading to its limited applicability in completing a grant application under the PAR-18-407 announcement.

The video on the NIH website provides an excellent introduction to the NIH mission, how to look for grant announcements and the general grant submission and review process. The author of this paper recommends that all Principal Investigators irrespective of experience level review this webpage initially to help get an idea of the work involved in proposal preparation and to plan their approach to completing the PAR-18-407 application appropriately. These pages can help with organizing the grant writing effort and provide the PI with ideas on preparing a master checklist.

¹⁰ “Grant Writing Tips Sheets,” National Institutes of Health, last updated March 30 2012, https://grants.nih.gov/grants/grant_tips.htm

¹¹ “Preparing Grant Application,” National Cancer Institutes, Division of Extramural Activities , accessed February 2019, <https://deainfo.nci.nih.gov/extra/extdocs/apprep.htm>

The National Institutes of Allergy and Infectious Diseases recommend that the PI present the content of the application in a format that is easy for peer reviewers to understand the project's objectives. Peer reviewers are experts in their respective fields, and applicants must take the time to understand their audience and prepare the application layout to hold the reviewer's interest.¹² Careful attention should be paid to the level of language used; the objective of the proposal and the overall format of the application so that the information appears cohesive and follows a logical order.

The Scientific Review officer chooses members of the Scientific Review Committee (Committee) and assigns applications for review.¹³ Each Committee comprises of a Chair who leads the discussion and moderates the meeting while also reviewing any specific applications assigned to them for review. The rest of the Committee includes individuals accomplished in the areas of the applications submitted for review. Reviewers receive the application packet approximately six weeks before the meeting date and are expected to critique and score the application as well as prepare comments for discussion. All Committee members are expected to maintain the confidentiality of the proposals and to disclose any conflicts of interest related to applications assigned to the Committee. For each application assigned to a Committee, three reviewers namely the primary reviewer, the secondary reviewer, and a general reader will review the submission thoroughly and be knowledgeable of the entire application. The primary reviewer will lead the discussion at the review meeting, and the other Committee members will provide feedback and engage in a discussion on the

¹² "Know your Audience," National Institute of Allergy and Infectious Diseases, last updated April 14, 2017, <https://www.niaid.nih.gov/grants-contracts/know-your-audience>

¹³ "Peer Review," National Institutes of Health, Office of Extramural Research, last updated December 11, 2018, <https://grants.nih.gov/grants/peer-review.htm#Initial>

merits and drawbacks of the application. The applicant's aim should be to provide enough information for the three reviewers to be able to discuss strengths and weaknesses and answer any questions raised at the meeting. The application should also be succinct and well written for other reviewers on the Committee to grasp the concept in the short time they spend looking through the application in preparation for discussion. The FOA includes criteria for review and scoring, and this has dual intent. It helps the PI build the application using the review criteria as a guide. It also provides reviewers with a framework to assess and score the application by defining information that they should expect to find in the submission.

The Falk-Krzesinski and Tobin article on the different review criteria between Federal Grant funding agencies provides a brief comparison of metrics and section content on NIH, National Science Foundation (NSF) and National Endowment for the Humanities (NEH). While the PI may not find a comparison between all three agencies useful in completing an application to the PAR-18-407 announcement, it does add to the knowledge on NIH criteria individually and provides a quick snapshot of the main components for inclusion in the Research Strategy section of the application.¹⁴ Principal Investigators often apply to several federal agencies for funding and the author of the article cautions that an understanding of the review criteria for each agency is critical to be able to develop application content appropriately for the chosen announcement. If the PAR-18-407 submission is not streamlined based on the FOA requirements, it will not be scored favorably by the reviewers based on the scoring guidelines provided to them. This

¹⁴ Holly J Falk-Krzesinski and Stacey C Tobin, "How Do I Review Thee? Let Me Count the Ways: A Comparison of Research Grant Proposal Review Criteria Across US Federal Funding Agencies," *The Journal of Research Administration* (46)2, 2015

article simplifies each NIH review criteria by translating them into common questions, the answers to which can fulfill the review requirements.

The criteria related to significance translate into the importance of the project objectives and must address the current limitation in the chosen area of research that the project will address. In the innovation section of the research strategy, the article suggests that the submission include how the proposal stands apart from current practices in the area of research by describing new and novel methods and processes.

For the criteria related to approach, reviewers need to understand the methodology and pathway to achieve project goals from the information provided. The information should cover the approach on the experimental/ research front as well as the supporting and existing data which channelized efforts towards the chosen approach in an attempt to enhance current knowledge.

The pursuit of submitting a grant is associated with several myths shared between researchers based on their own experiences with grant writing. Kenneth Henson's blog addresses and debunks some myths associated with the grant writing process and are included as grant writing tips in the manual.¹⁵ The blog discusses the myth that fewer grants are being funded due to the shrinking pool of federal funds and that only large institution with prior federal funding win grants in every cycle. To debunk these myths, the blogger states that federal funding remains a viable option to support research activities and federal agencies are keen on supporting strong research projects.

The manual assists with writing a strong proposal to help the PI obtain funding successfully in their first attempt. Additionally, institutions and researchers proven to be

¹⁵ Kenneth T Henson, "Debunking Some Myths About Grant Writing," Chronical Of Higher Education, June 26,2003, <https://www.chronicle.com/article/Debunking-Some-Myths-About/45256>

good stewards of federal funding can showcase their success on the facilities and resources page or the PI's biosketch section of the application. The blog also addresses the myth that connections are required within the research community to help obtain funding successfully. In light of this information from Henson, the manual recommends that Principal Investigators establish collaborations with other researchers and constitute an Executive Committee to assist with review and feedback on the application. To debunk the myth that meeting the submission deadline is the measure of successful grant writing, the manual notes that applying to the right agency and submitting a strong proposal should be the primary focus of the PI. The manual notes that submission deadlines are non-negotiable and provide instructions on being organized and creating a quality proposal within expected timelines.

The manual aims to help Principal Investigators target specific content for each section of the PAR-18-407 application without duplicating information. The NIH-FDA protocol template released in 2017 has been consulted to incorporate instructions related to human subjects' protection, safety assessments and biostatistics in the manual.¹⁶ Upon successful funding, these sections from the application can be incorporated into the clinical trial protocol and eliminate the need to develop content separately.

The NIH grant application form SF424 was used as a primary resource in building the checklist and application instructions in the manual. As instructed by the NHLBI,

¹⁶ "Clinical Trials E-Protocol Tool and Template Documents," Office of Science Policy, National Institutes of Health, accessed February 2019, <https://osp.od.nih.gov/clinical-research/clinical-trials/>

specific requirements of the PAR-18-407 announcement were incorporated into the checklist and manual.¹⁷

The SF424 general format includes instructions for submitting training, fellowship, career development, multi-project, small business, and research applications and is extensive and challenging to follow. Since the PAR-18-407 FOA requires the completion of the research format of the SF424, the Principal Investigator should access this format on the NIH website. This format provides instructions on completing each section of the research SF424 application form. The instructions also include web links to other areas of the NIH website where information, policies, and guidelines can be accessed to complete the grant application. The final pages of the research SF424 format include snapshots of the actual forms. While the SF424 is the primary source for instructions on completing each question of the application form, instructions within the FOA always take precedence if individual sections have different expectations and requirements for review. The Principal Investigator is required to assimilate instructions from the SF424 and the FOA and complete the application correctly. The author of this project has reviewed and compared the SF424 and the PAR-18-407 FOA and combined instructions to create the manual and checklist.

The author of this project also reviewed various locations within the NIH website to understand common errors and failures associated with the grant application process.¹⁸ To establish the tone of the manual and cater it to the researcher, the author read blogs

¹⁷ “Research Instructions, Guidance for Research Only, SF424 (R&R) version E” How to Apply- Application Guide, National Institutes of Health, revised 7 December, 2018, <https://grants.nih.gov/grants/how-to-apply-application-guide.html>

¹⁸ “Common Mistakes in Writing Applications,” National Institute of Mental Health, accessed February 2019, <https://www.nimh.nih.gov/funding/grant-writing-and-application-process/common-mistakes-in-writing-applications.shtml>

and websites from other researchers documenting their personal experiences. These are included in the references on this project paper

Chapter 3. Need(s) Assessment

3.1. Establishing the Need for a Manual

The NHLBI provides several materials to approach the grant application process. However, researchers also acknowledge that the submission process is sometimes mastered through trial and error and by obtaining feedback from seasoned and experienced peers.

The author of this project was presented with an opportunity to assist a PI affiliated with a local university in submitting an NHLBI grant in 2015. The author had no background in submitting proposals and relied on prior research administration experience to dissect the application requirements and construct a strong submission. Understanding the nuances of grant submission took a considerable amount of time while the application was prepared in parallel. The author was simultaneously attending courses in the Master of Science in Research Administration Program at Johns Hopkins University and was exposed to grant writing tools and knowledge sharing with classmates. While students in the program came from varied backgrounds and experiences with grant submission, it was a universal theme that not many had attempted to submit grants to the NIH or could find tools to help them approach a submission systematically. It was noted through discussion boards that most students would approach the SPA at their respective universities to initiate an NIH grant submission. In regions outside the US, university infrastructure varied to be able to provide such assistance.

Through these interactions, literature review related to the grant submission process and from personal experience, the author chose the topic of writing a manual to

guide research applicants through the NHLBI submission process using the PAR-18-407 announcement as a template.

3.2. Metrics for Needs Assessment

The author's experience while working on the grant application, the assistance obtained from the NIH Program Officer and university administrators and examples available through the NIH website clearly showed that there are no standalone resources available to assist a researcher to complete an NIH application systematically. The need for a step by step instruction manual using an NHLBI announcement was the primary metric used to establish the outcome of this project.

3.3. Resources Aiding Needs Assessment

The manual is designed to help Principal Investigators complete an NIH PAR-18-407 grant application. The author chose to obtain guidance from the Principal Investigator and collaborators that came together to submit the grant application to this announcement at the local university in 2015. The physicians primarily developed sections of the application related to scientific content. The author was responsible for developing the administrative sections of the application and sought assistance from seasoned grants administrators at the applicant university. Input received from biostatisticians on the team, the NIH Program Officer and agency Budget Analyst has been included as content on the manual. Research associates on the PI's team at the local university who developed and reviewed individual sections of the application also provided input into this project. Classmates and Professors at Johns Hopkins University,

Master of Science in Research Administration Program have provided material that was found useful in the development and completion of this project

Chapter 4. Project Description

This project involves the creation of a manual to apply to the PAR-18-407 NHLBI funding announcement. The manual includes steps in organizing the PI and research team's time and effort after a funding opportunity announcement is identified and before the application process begins. The manual opens with an introductory section which describes the layout of the manual and the information covered to support a PAR-18-407 submission. It begins with the process of initiating a discussion with the applicant's university officials on the PI's intent to apply for NHLBI funding. Discussion topics such as the applicant institution's eligibility to apply to the chosen FOA, its ability to support the PI and provide resources during the application process and throughout the project period are included in this chapter.

The manual includes details for the PI to contact the NHLBI Program Official and discuss the proposal submission. For project budgets greater than \$500,000 direct costs in any given year of funding, the manual will provide instructions on preparing for an NIH staff consultation meeting by including a sample PowerPoint template with key discussion points. The manual will also discuss the process for submitting a revised letter of intent incorporating feedback from the staff consultation meeting and obtaining an NHLBI acceptance letter to submit a full application.

The manual also covers instructions on approaching the Food and Drug Administration (FDA) for review and determination for the need of an Investigational Device Exemption (IDE) or Investigational New Drug Application (IND) for new drugs, new indications or expected label changes based on project outcomes.

The manual uses the SF424 document and the PAR-18-407 program announcement to help construct the full application. In moving through each section, the manual describes page limits and the inclusion of content while incorporating feedback from previous scientific reviews of an application submitted by the author to this announcement. The manual includes instructions for developing the scientific content of the proposal for sections such as the specific aims, a project abstract, research strategy, biostatistics and project narrative. Descriptions for the administrative sections of the application such as the details on facilities and resources, sub-awards for collaborators, human subjects' protection, and project timelines, selecting a single IRB for multi-site projects, data management, and dissemination plan are included. A description of the details related to completing an NIH biosketch document, Research & Related (R&R) budget page, and associated justification is covered in the manual. This section on budget development includes possible budgetary items as well as a sample budget template and information on indirect costs.

The manual provides common system errors upon official submission of the application and a brief overview of the NHLBI review process. A sample checklist for the PAR-18-407 announcement is included to assist the PI and provide a snapshot of the entire application for easy reference and track the progress of application development.

Chapter 5. Methodology

5.1. Methodology

The approach to gathering content for the manual includes the author's personal experience in completing an NHLBI grant submission and resubmission to the PAR-18-407 announcement along with materials and discussions with students in the Master of Science in Research Administration program at Johns Hopkins University. Several notes prepared during the grant submission process, review of the FOA requirements, interacting with an academic research organization in developing the proposal, consultants and sub-awardees have provided the author sufficient exposure to the application process. Discussions on common grant application challenges and review of articles in the grantsmanship toolbox completed as part of the course work at Johns Hopkins University have also contributed to the development of this manual. Articles on the experiences of other applicants provided valuable lessons on avoiding pitfalls. The manual is an assimilation of lessons learned through the years and aims to create a comprehensive and easy path for researchers to follow while submitting a winning proposal to the PAR-18-407 announcement.

5.2. Design of the Manual

The manual includes eight chapters and is designed to assist applicants to complete an entire SF424 project application in response to the PAR-18-407 announcement. Chapter 1 is an introduction describing the intent of the manual and topics covered in the document.

Once the PI decides to apply to the PAR-18-407 announcement and before the actual application process begins, specific preparatory tasks must be completed. These tasks have been covered in Chapter 2 of the manual. This chapter discusses the process to approach the Sponsored Programs Office at the applicant university and the importance of these initial discussions. The PI should ensure the upper administration at the applicant university is supportive of the project idea and that the institution is eligible to apply for funding. It also discusses the importance of evaluating the resources required to execute the project if the grant funded. The chapter discusses the process of contacting the NHLBI through the agency Program Officer and preparing for these initial and subsequent contacts as necessary. For project budgets greater than \$500,000 direct costs in any given year of funding, the NHLBI requires a staff consultation meeting between the PI and key NHLBI department members. The manual guides on preparing for this staff consultation meeting which involves a presentation on the project highlights followed by an interactive session with questions and critiques. The manual appendix includes a PowerPoint template, noting the discussion points for presentation at this staff consultation meeting. Guidance on incorporating information and feedback obtained during the staff consultation meeting and how it should translate into submitting a revised letter of intent and obtain an NHLBI acceptance letter to submit a full application are included in this chapter of the manual.

Chapter 2 discusses the need for creating a steering committee or Executive Committee (EC) to lead the proposal. Selecting the right number of people with diverse expertise is essential and must be given sufficient time and thought to set the application process on the right path. Principal Investigators often delay approaching collaborators or

forming an EC. Incorporating appropriate feedback from the members of the EC allows a broader set of perspectives to be included on the application and meet the different needs of individuals on the Scientific Review Committee. Executive Committee members should often meet during the development of the application and discuss data to be included, review sections of the application critically and impartially and stay abreast of publications and advancement in the proposed area of research. This holistic approach prevents essential information and developments from being overlooked which could affect scoring during the review process.

Chapter 2 also addresses the process for contacting the FDA to determine its role in providing oversight of the clinical trial required by the FOA. The PI must exhibit due diligence with approaching the FDA and discuss the requirements of an Investigational Device Exemption or Investigational New Drug application. Most investigators are apprehensive about involving the FDA, and completing this step early in the application development process prevents surprises during the NHLBI's review of the grant when FDA review is identified to be mandatory. The process of approaching the FDA officials and aid in their review by providing appropriate project-related information is covered in Chapter 2.

Vendors and scientific collaborators from outside the applicant institution in addition to the PI and his/her staff may be involved in the project. Chapter 2 covers the vendor identification process and its role in the development of the grant application. Collaborators and vendors are paid with grants funds through sub-awards or contracts with the applicant institution. Sub-award paperwork and vendor support letters outlining their role, commitment and budget should be included on the grant application.

The FOA requires that key project personnel set up an electronic Research Account on the eRA Commons website. Chapter 2 discusses the importance and the process of account set up and the inclusion of the eRA Commons username on the NIH biosketch for these individuals.

Chapter 2 of the manual completes its discussion on grant preparatory tasks with instructions on creating a checklist for this FOA. The checklist allows the project team to remain organized and is a quick reference guide to the content required for each section of the application. A sample checklist used by the author on the PAR-18-407 application is included as an appendix to the manual and can be modified by users of the manual depending on the roles within the grant submission team and applicant institution requirements.

Chapters 3 through 6 of the manual provide instructions on completing the scientific and administrative sections of the SF424 application and FOA requirements. The manual refrains from providing instructions on completing basic information such as names and addresses of the applicant institution on the SF424 form. These fields are self-explanatory and completed by university SPA officials.

Chapter 3 addresses the scientific components of the PAR-18-407 announcement. It begins with the descriptive title and includes the requirements for a project summary/abstract and a project narrative. Some of these sections get included in the NIH database for access by the general public. Each of these sections has word limits and must be written at a specific language level to be incorporated into the NIH database and appeal to an audience of non-scientific readers. This chapter also provides instructions on

creating the bibliography or references section of the application and includes all articles and sources consulted in building the project and the proposal.

The specific aims and research strategy are important sections of the grant application. They should clearly state the objectives, design, and execution plans of the project. The final section of this chapter addresses the statistical design and power of the project. The biostatistical approach of the project should be reproducible by independent biostatisticians reviewing the proposal, and the project should use standard statistical tools and methods. This section influences the scope of the project by dictating the number of patients to be enrolled in the clinical trial, the size and duration of the project and its budget. A poorly defined biostatistical plan can derail the entire proposal with reviewers coming away with more questions on the project outcome, than answers it will provide as generalizable knowledge to the clinical community.

Chapter 4 covers the administrative sections of the PAR-18-407 application and includes the cover letter, facilities and resources at the applicant institution, equipment used on the project, structure of the project team, and the recruitment and retention of subjects in the clinical trial. NIH multi-site clinical trials require a single IRB to provide ethics oversight to reduce project budget and minimize the timelines for review. Chapter 4 includes details on identifying a single IRB or obtaining a waiver when more than one IRB oversight is required.

The data and safety monitoring section of Chapter 4 describes clinical trial data management including its periodic review and monitoring for safety trends. The importance of a data safety monitoring board and the process of data review by this committee has been described in this chapter. The chapter also includes a description of

the data dissemination and resource sharing plan. The study timelines document on the grant submission should describe how and when important project milestones will be achieved. The NHLBI needs assurance that project progress will be tracked closely to identify delays and implement mitigation strategies.

A specific requirement of the NHLBI application is the need to include the biographical sketch for project key personnel using the agency's biosketch template. Chapter 4 of the manual discusses the information required on this document and provides a sample biographical sketch for the PI as an appendix.

To submit a strong proposal indicating a supportive group of multi-site investigators and collaborators, the FOA requires the submission of letters of support from these individuals. Chapter 4 includes instructions on obtaining letters of support and provides a sample letter of support in the manual appendix.

Budget development can take weeks to complete, as it may need to include budgets for multiple clinical sites as well as essential components such as salaries, reimbursement to participating sites and patients, IRB review, the cost for meetings, travel, equipment, and supplies. The PA-18-407 FOA supports projects for a maximum period of 5 years and an extension for the sixth year may be requested by providing strong justification. Thus, the budget section of the manual in Chapter 5 covers steps to build a project budget for each year of funding. The information related to the base salary and fringe and benefits for personnel at the applicant university may be requested from the university human resources department. Each individual's salary support requested through the grant must be calculated based on their time commitment to the project. The government approved per-diem rates should be used to calculate travel costs and

expenses related to project supplies. Sub-award paperwork may be required for consultant and collaborator reimbursements. These requirements can add several steps to the budget development processes and should be planned appropriately. The manual helps assign dollars to common budget line items and provides a sample budget for year one that can be duplicated for subsequent years of funding. This is included as an appendix in the manual. The grant application also requires a budget justification document explaining the dollar support requested for each line item on the project and this is included in Chapter 5.

Chapter 6 of the manual covers information on human subjects' protection, which is required in the application. It addresses risks to human subjects, the need for incorporating adequate protection of participants in the trial design, and the risk-benefit ratio of subject participation and generalizable knowledge gained from project outcomes.

Chapter 7 of the manual reviews the actual submission process and standard error messages received from the electronic grant submission portal. It provides a brief overview of the process and outcomes of the scientific review. The manual concludes in Chapter 8.

In summation, the manual includes instructions on presenting essential information graphically where applicable. The entire layout of the manual has been intentionally kept simple and written in a format which is easy to follow. It is intended that PI will find all information required to complete each section of the application with ease by following the manual. This approach will help the PI to stay organized, focused, save time and reduce the chance of missing critical information that needs to be included in the proposal.

Chapter 6. Project Results and Discussion

The outcome of this project is the creation of a manual to assist Principal Investigators in completing an entire application to the NHLBI announcement: PAR-18-407. Throughout the application process and during discussions with students at Johns Hopkins University, the author has been aware of the need for a manual which provides step by step guidance on completing an NHLBI grant application. The literature reviewed has acknowledged the challenge of planning and completing an NHLBI application. While the task of applying for a grant is cumbersome, time spent in finding guidance on the application process often results in very little concrete guidance on embarking on a logical pathway.

The author's first-hand experience has influenced the instructions included in the manual. The checklist provided as an appendix to the manual can be used to complete each section of the application. By customizing the checklist, it can be used by researchers to apply to different NIH grant announcements as well.

Information on the NHLBI Scientific Review processes available online and through discussions with the agency Program Officer has resulted in the manual providing instructions to the PI on writing a sharp yet succinct proposal.

Based on the research done to create this manual and challenges faced from experience with the application process, the author of the project has the following recommendations for Principal Investigators who wish to apply to the NHLBI PAR-18-407 announcement:

Recommendation 1: Developing an effective plan for grant writing

The first step in obtaining funding is to complete all requirements of the application and submit it within the specified timeline. The need to juggle various commitments and assimilate project components in the application stage is an important indicator of the PI's ability to deliver project objectives once funded. Mismanagement of time results in a haphazard and tardy submission and questions the PI's ability to being a good steward of federal dollars. The manual helps the PI to visualize the entire proposal and develop its components within the submission deadline.

Recommendation 2: Writing with clarity

The grant application should convey the intent of the project, gaps in knowledge it will address and how its objectives will be achieved. The cost of reaching the project goal should be clearly stated within the abstract as well as detailed in sections of the application. The entire submission should be logically presented without information contradicting itself. The proposal should pique the reviewer's interest in the project objective and outcome and eliminate ambiguity related to project intent or its execution. The manual includes instructions on information to be included within each section of the application to help establish a logical flow of content.

Recommendation 3: Establishing collaborations

The PI can choose to either collaborate with peers and experienced mentors to obtain guidance and feedback throughout the application process or involve collaborators as key personnel on the grant application. Building lasting relationships and maneuvering through the assignment of project roles with key stakeholders must be initiated early.

Clarity on project objectives helps filter feedback from collaborators and mentors and avoids too many ideas being included on the grant thereby making it lackluster and appearing directionless.

Chapter 7. Conclusion

Grantsmanship is a competitive field and applications which are written well and convey project intent, design and outcomes clearly, often receive funding. With its commitment to using federal dollars to support breakthrough medical research, agencies like the NHLBI seek to define clear pathways for their review and decision-making processes in supporting grants. Soliciting specific content on a grant application ensures all submissions include the necessary information needed by the agency for review. Therefore, an applicant's presentation and writing skills play a crucial role to help distinguish between competing applications during the review cycle. Reviewers are expected to score submissions based on the content provided, and this poses the biggest challenge to the PI. The critical step in the long and challenging process of grantsmanship is ensuring the right approach is adopted with the help of a dynamic grants administrative team. The grant application manual was developed to assist with making this process less stressful and more robust.

The author hopes that using the manual and appendices as a guiding tool will help researchers in completing an NHLBI application to the PAR-18-407 announcement. The manual seeks to provide general tips to help initiate and complete the grant application and aid the PI in planning their time and effective use of resources with meeting submission deadlines.

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**Appendix 1. A MANUAL FOR APPLYING TO THE NIH COLLABORATIVE
UG3/UH3 CLINICAL TRIAL ANNOUNCEMENT: PAR-18-407.**

The Manual begins on the next page.

**A MANUAL FOR APPLYING TO THE NIH COLLABORATIVE UG3/UH3
CLINICAL TRIAL ANNOUNCEMENT: PAR-18-407**

Preeti P Kamath

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List of abbreviations	
CCC	Clinical Coordinating Center
CRF	Case report Form(s)
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
EC	Executive Committee
eRA	Electronic Research Administration
F&A	Facilities and Administration
FDA	Food and Drug Administration
FOA	Funding Opportunity Announcement
NHLBI	National Heart Lung and Blood Institute
NIH	National Institutes of Health
PAR	Program Announcement Receipt
PDF	Portable Document Format
PI	Principal Investigator
PMC	PubMed Central
PMID	PubMed ID
RFP	Request For Proposal
SF	Standard Form
SPA	Sponsored Programs Administration
SRO	Scientific Review Officer
TBD	To Be Determined
URL	Uniform Resource Locator

Chapter 1. Introduction

The National Institutes of Health (NIH) is a Federal agency created to support medical and health-related research on an international scale. As a division of the U.S Department of Health and Human Services (DHHS), the NIH is synonymous with funding projects which have contributed to large scale medical breakthroughs, both in clinical practice as well as in basic science research.

The NHLBI is an NIH Institute which works with scientific projects related to cardiovascular, respiratory and blood diseases. The Institute solicits proposals for research funding several times a year based on the agency's funding cycle. Researchers all over the world are beneficiaries of this funding and vie for limited dollars to help advance their scientific work. The Institute releases Funding Opportunity Announcements (FOA) seeking proposals for review through their pre-defined and transparent peer review process by the Scientific Review Committee. The NHLBI ensures that relevant and consistent information is submitted for review through the use of the Standard Form (SF) 424 and submission process. While the form itself has a general format, individual sections and components may vary depending on the type of funding sought. Applicant institutions and Principal Investigators (PI) must submit their proposal using the appropriate SF424 application and federal grants websites such as www.grants.gov .

This manual outlines the approach to submitting a grant to an NHLBI FOA: PAR-18-407: Clinical Coordinating Center for Multi-Site Investigator-Initiated Clinical Trials (Collaborative UG3/UH3 Clinical Trial Required). This announcement is associated with a companion announcement PAR-18-410: Data Coordinating Center for Multi-Site

Investigator-Initiated Clinical Trials (Collaborative U24 Clinical Trial Required). Note that the NHLBI expects the clinical coordinating center (CCC) and data coordinating center (DCC) to function independently of each other in terms of data collection and management. This separation is intended to limit the exchange of data between the two centers and minimize bias in trial conduct and outcome. The NHLBI also expects the centers to work together and execute the project with precision. Therefore, certain sections of both applications may have overlapping content to address this requirement.

The manual works through the scientific and administrative sections of the application and provides instructions on the content to be included for each section. It assimilates the requirements of the research SF424 form and the PAR-18-407 FOA. Completing the basic information of the SF424 form will not be covered in this manual as the information collected is standard across all grant submissions to the NIH and the questions are self-explanatory. The applicant university staff should be well-versed with completing basic information on the form.

The manual also includes the submission process and possible outcomes of the review by the NHLBI. Sample templates for key documents such as the cover letter, budget, study timelines, participating site support letters and survey, biographical sketch for the PI and project team organization have been provided as appendices to the manual. A master checklist is also included to help track submission requirements.

Chapter 2. Grant Application Preparatory Tasks

2.1. Approaching the applicant university research administration

The PAR 18-407 announcement requires that the application is submitted on behalf of a Principal Investigator by their affiliated institution (E.g., University). The applicant institution must play an important role in all aspects of application development. Through mutually agreeable discussions, tasks involved in this submission process may be assigned amongst various stakeholders such as the PI, collaborators, and University Sponsored Programs Administration (SPA) associates. However, the Principal Investigator remains in charge and is responsible for driving the entire process to completion.

To ensure that all parties involved are aligned with the goals, objectives, and timelines of the proposal, the PI should undertake the following tasks:

- Set up a meeting with university officials to include administrators within the Sponsored Programs Administration (SPA) office. This meeting will begin with a discussion on the PI's intent to apply to this FOA and help determine the institution's eligibility to apply for funding.
- The discussion should cover the project idea and deliverables and identify resources required for project execution.
- Once the decision is made to proceed with applying, a SPA administrator may be assigned to assist with application development. There should be agreement on the method and frequency of communication between the PI and the SPA

administrator: e.g., meeting once a week face to face or via conference call and continued e-mail communication or ad hoc meetings/calls between weekly standing meetings. These meetings help set tasks to be accomplished each week and review their progress. They also provide an opportunity to discuss challenges encountered during application development.

- The SPA administrator will discuss the internal institutional deadlines for submission of various components of the application. The administrator will review each section and then the entire application to validate administrative content and ensure that there are no red flags with the proposal.

2.2. Approaching the NHLBI

Once the applicant institution and PI agree on applying to the PAR-18-407 announcement, the PI should contact the NHLBI Program Officer associated with the FOA. This initial meeting is done via conference call, and the discussion should involve the following:

- Details of the project being submitted to this FOA, applicant university details such as name and location and the intended deadline for submission.
- The PI should prepare to ask questions related to the NHLBI submission process and specific content to be included on the submission. The Program Officer will share information and resources to help the PI prepare for submission.
- If the Program Officer deems the meeting to be successful and would benefit from further discussion, a second meeting involving scientific/ research members from within the NHLBI Division of Cardiovascular Sciences will be arranged.

Participants at this meeting can include agency biostatisticians, project management officials and budgetary experts who are well-versed with agency expectations, the review process, and project execution requirements. Feedback obtained during these discussions is essential in eliminating multiple rounds of edits and revisions throughout the submission process. A member of the PI's team should be designated to take minutes during these meetings.

- Once the proposal is deemed to hold merit warranting a full application and if the proposal expects to spend \$500,000 USD or more in direct costs in any given year of funding, the Principal Investigator will be invited to a staff consultation meeting at the NHLBI office by the Program Officer.

2.3. Staff Consultation meeting at the NHLBI

If the PI is invited to a staff consultation meeting due to the project's costs noted above, then the first step after initial discussions is to prepare for a staff consultation meeting with the NHLBI. This meeting is required to obtain the NHLBI's approval to submit a large grant for review. It includes a formal meeting between key stakeholders within the NHLBI Division of Cardiovascular Sciences and members of the Principal Investigator's team and could be arranged in person or via conference call.

Preparations for this meeting should be thorough and meticulous with a focus to highlight the project, ask questions and engage in discussion with NHLBI decision makers. The following approach is useful:

- Draft a Letter of Request including details of the project such as the project title, applicant institution, FOA number, project objectives and outcomes, project

execution plan, budget for each year of the project, sample size, and duration of the project. Include the names of key project personnel and the expected application submission date in the letter. Also, include the specific plan for sharing project results with the clinical and public audience and how data will be shared. Submit the letter to the NHLBI Division Head through the Program Officer by the deadline mentioned on the NIH website. The letter of request **should not exceed five pages**, and it is advisable to submit this draft letter approximately 24 weeks before the intended full application deadline

<https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/applications-with-direct-costs-of-500000-or-more-in-any-one-year>

- Within a few weeks of receiving the letter of request, the NHLBI program Officer will notify you of a decision on whether the agency is willing to allow the application to be submitted. If you are selected, you and the research team will be invited to a staff consultation meeting.
- If the meeting is in-person, identify 2-3 important members of the project team to accompany the PI to the meeting location. Additional team members may be invited to attend and support the project via a conference call. The NHLBI Program Officer can help with setting up a conference call number and coordinating meeting logistics.
- Staff consultation meetings are usually 60 minutes in length. Various members from the NHLBI attend the meeting depending on availability. The Program Officer and Scientific Review Officer assigned to the FOA are generally present. Additional members such as the Head of the Division of Cardiovascular

Sciences, the NHLBI biostatistician, officers and administrative personnel such as budget experts and project management experts may be present. These individuals are well-versed with the application process and agency policies as well as review scientific committee feedback and therefore a well- prepared presentation from the Principal PI is a must.

- Prepare meeting slides to present project details for approximately 30- 35 minutes. Ensure content is precise but comprehensive and covers topics included on the letter of request previously submitted.
- Handouts may be provided, however the NHLBI appreciates the careful expenditure of dollars even in the pre-submission phase.
- Once the slide set is ready, the PI should request collaborators and SPA administrators to review and provide feedback as different perspectives can help make the presentation stronger. A sample template for the slides is provided in Appendix II
- After the presentation by the PI, the rest of the hour includes a discussion between members present at the meeting. This involves questions from the NHLBI staff on the project objectives, execution plan, budget as well as project size and biostatistics. The PI should be prepared to answer questions and explain the approach to the project. Suggestions may also be put forth by the NHLBI members. The PI should be open to feedback and criticism, and a designated member should take detailed notes during the discussion. This meeting is also the opportunity for the PI to ask the agency members questions and seek clarification on the submission process or the proposal.

- Following the meeting, the PI must modify the letter of intent incorporating the feedback received and resubmit to the NHLBI not more than 12 weeks before the intended application submission deadline. The NHLBI will respond within two to six weeks of the receipt of this letter with a decision to allow the applicant to submit a full proposal. This decision is released in the form of a letter that includes details of the project, and the budget cap for the project. Note that the time available between receipt of this acceptance letter and the submission deadline for the full proposal can be as short as six weeks and hence the PI must remain in contact with the Program Officer to ascertain the agency's receptiveness to receiving a full application. The PI should begin preparing content for the full application simultaneously while the decision is awaited.
- Once the official invitation letter is received, the PI should review the contents of the letter to ensure the information included is accurate. Any discrepancy should be addressed immediately with agency staff and a final letter obtained. This letter must be included on the final submission, and it is crucial that it reflects the correct information. Note that receipt of a staff consultation or a letter of acceptance does not guarantee funding. It only allows the submission of a full grant application for consideration by the scientific review committee and the NHLBI.

2.4. Approaching the FDA

If the proposed project will include investigational drugs or devices or new indications of marketed products, the FOA recommends that the pre-IND or IDE meeting with the FDA be completed before the application is submitted for peer review. The

outcome of this meeting with the FDA must be included in the NHLBI application. If the FDA determines that a full IND or IDE application is required for their review, information on how this will be accomplished, and the expected its timeline must be included in the NHLBI submission. The pre-IND or IDE discussion with the FDA can be initiated as follows:

- Create a project synopsis document including key details of the clinical trial.

Most components in this document will include information from the letter of intent and the NIH staff consultation slides. Ensure the document sent to the FDA clearly states the request and outcome being sought from their review. Submit this document to the FDA using the appropriate contact listed on the agency website and follow-up with a phone call. The FDA is an approachable agency and is willing to schedule a conference call to discuss the project. Due to competing priorities and time constraints, this process could take a few weeks, and it is essential to contact the FDA early in the application process. If the FDA determines the project does not require an Investigational New Drug (IND) or Investigational Device Exemption (IDE) application, the agency will confirm the same via a letter faxed to the PI. This letter can be included with the grant submission packet to indicate to the reviewers that due diligence has been done in consulting the FDA. If the project idea changes during the development of the grant application, the FDA may need to be consulted again to confirm the exemption carries through.

- If the FDA determines that an IDE or IND application is required, further consultation with the agency should be scheduled, where a timeline for

submission and approval is discussed. This information and the plan to obtain full approval from the FDA should be included on the grant. The NHLBI expects to review these timelines before a funding decision is made, to ensure the project start will not be delayed once funding is released. The PI must also confirm with the NHLBI Program Official that the proposed timeline is reasonable and acceptable to the agency in consideration for funding.

2.5. Setting up an Executive Committee

An Executive Committee (EC) functions as a steering group for the project. This committee should be formed as soon as discussions with the NHLBI Program Officer begin. The EC should be comprised of experts in the field of the project topic. Depending on the size of the project, the number of committee members may vary. The committee is led by the Principal Investigator and can include 4-5 physicians, the lead biostatistician and the project manager. At least two members of the EC should be present in person along with the PI at the NHLBI staff consultation meeting, and additional EC members can be invited to join the staff consultation meeting by phone.

Once the decision is made to proceed with submitting a full application, the PI can ask members of the committee to participate in writing or reviewing application sections. Regular EC calls should be held to discuss the progress of the application, content for inclusion, any challenges foreseen with project execution or to obtain feedback from experts on the Committee. The EC members contribute as the first round of critical reviewers and accepting their viewpoints for discussion can help strengthen the application significantly. If any of the EC members are to be compensated for their time on the project through the grant budget, a sub-award should be initiated with their parent

institution. Note that EC members may not always be considered key personnel on the project based on their contributions and commitment and the need to submit their NIH biosketch should be evaluated accordingly.

2.6. Collaborators and sub-awards

At the initiation of application development, project collaborators within or outside the applicant institution may be identified.

Collaborators outside the applicant institution:

- Vendors who can provide services or products should be identified through a Request for Proposal (RFP) process, and the SPA administrator assigned to the project can aid in this regard.
- Once responses to the RFP are received, vendors and services should be finalized, and representatives from these companies should be included in the application development process. Vendors often provide information about the product and its role in enhancing the project being considered for funding.
- Obtain a budget and support letter from the vendor to include on the grant application.
- For collaborators at other institutions, the SPA will initiate sub-award paperwork between both institutions and this will include the scope of work and acceptable budgetary allocations. Note that collaborator budgets have specific requirements on how they are included as direct and indirect costs on the final application.

Once a grant is funded, significant deviations to sub-award allocations from the

initial submission are rarely acceptable to the NHLBI. Therefore, the PI and applicant institution must negotiate and reflect sub-award costs accurately.

Collaborators within the applicant institution:

- Budgetary allocations for collaborator salaries commiserate with their time and effort on the project must be discussed with the SPA administrator. Institutional policies may limit collaborator participation to ensure their institutional responsibilities are balanced. Misrepresentation of these areas on the grant application can become significant findings during project audits and affect an institution and individual's ability to apply for future funding or participate in other projects.

2.7. eRA Commons system accounts

This FOA requires that the PI and all key personnel have eRA Commons accounts set up before the application submission. Most universities have an institutional account and employees must request their individual account through the university. The PI and key research team members must initiate account set up before the application process is initiated. It could take several weeks for account set up, and the process should run in parallel with application development. Once the account is set up, users obtain their login credentials (username and password) via e-mail. This account user name is required to be included on the NIH biosketch and submitted with the application.

The eRA Commons account will also reflect application submission status, its assignment to a scientific review committee and meeting dates, scores obtained and the review

summary statement. The agency does not send status updates by e-mail; hence access to the eRA Commons account is essential.

2.8. Creating a checklist

While the letter of intent is under review with the NHLBI, it is recommended that the PI begin working on the full application. A submission checklist should be created to include all components of the application from the FOA and SF424 form. The effort expended at this stage in reviewing all materials and guidelines related to the FOA and assimilating important points in a checklist is invaluable. A sample checklist is included in Appendix I of this manual.

Chapter 3. Scientific components of the application.

Most sections of the scientific components of the application are written separately and uploaded as PDF documents in designated sections of the final SF424 application form. The PI should be cautious in keeping track of the required formatting and page limits for each section, as disregarding these requirements can automatically disqualify the application once submitted.

Page limits and formatting instructions are included within each section of this manual and can also be found on the NIH website at <https://grants.nih.gov/grants/how-to-apply-application-guide/format-and-write/format-attachments.htm>

3.1. Descriptive title of project

- The project title must be 200 characters in length to include punctuation and spaces. The title will be typed directly on to the SF424 application. An acronym can be included, and this counts towards the character limit.
- Since this FOA is part of a cluster and paired with the PAR-18-410 announcement, the project title should include the number of the application in the cluster. It will help the NHLBI pair the correct number of applications together for review, e.g. A Randomized Double-blind study to determine the bleeding effects of (Drug Name) in Geriatric patients-1/2.

3.2. Project Summary/Abstract

- This section will be uploaded as a PDF attachment and has a limit of 30 lines of text.

- The content should include a brief description of the project to be undertaken and provide an accurate snapshot for readers to understand the what, why and how of the project.
- It should describe the long-term objectives, health relatedness and relevance of the project to the NHLBI mission.
- It should be written in language that caters to the non-scientific community and should not use the first person. Specifically, the information should include project objectives, size and duration, and measurement of outcomes.
- Do not include budgetary or confidential information on the abstract. This section will be placed in the NIH database and accessed by the public.

3.3. Project Narrative

- This section is submitted as a PDF attachment uploaded to the SF424 application.
- It should describe the public health relevance of the research project in 3 sentences. If funded, this section will be combined with the abstract for public release.

3.4. Bibliography and References cited

- There is no page limit to this section.
- All materials referenced and relevant to the project must be included in this section. If the article referenced falls under the Public Access policy, NIH Manuscript submission reference or PubMed Central (PMC) ID if available should be included. For articles that are in publication, indicate “PMC Journal -in process” against the reference.

- For articles that do not come under the Public Access Policy, the URL or PubMed ID (PMID) may be included along with the full article reference.

3.5. Specific Aims

This section is significant as an introductory piece to the project and must be compelling to pique the interest of the reviewer. It should include:

- A single page PDF attachment uploaded to the SF424.
- The content should include a concise description of the project goals, the objectives and expected outcomes and the impact of the results on the associated field of research.
- Identify if the project is testing a hypothesis, proposing a solution to a critical problem or providing evidence that could impact clinical practice.

3.6. Research Strategy

The research strategy is the foundation of the entire project. As noted in this section, the content of the research strategy describes the scientific intent of the project such as the primary and secondary objectives, the trial design, key components of the clinical trial such as inclusion/exclusion criteria and the processes to be undertaken. The sections of the research strategy provide insight and framework for each area of the project. It is advisable that this section be written first before other content of the application is developed. Spending adequate time on the research strategy is critical to developing a robust section which in turn sets the tone for the rest of the application.

The research strategy should be developed as a 12-page PDF document uploaded to the SF424 application. The section provides the PI with an opportunity to include key

aspects of trial conduct and human subject participation and must not duplicate information provided elsewhere on the proposal. The FOA requires this section to be broken down into subheadings and each subsection has specific instructions as follows:

- a. **Significance:** Explain the clinical trial importance and clearly state the question to be answered or the objective of the project. It should include the methods employed to test the hypothesis or meet the project objectives. The description must clearly explain the relevance of the project to current problems and the solutions proposed. The information should include why the project outcome would be relevant to the clinical community despite possible advancement in the field at the time of project results being available. Describe how the project results will advance clinical care to improve health care decisions and influence current practice trends.
- b. **Innovation:** This section must describe how the project seeks to be innovative in its approach and execution. New ideas or the use of current resources through an innovative approach should be explained here. This section should address expected challenges with testing this innovative approach and the plan to overcome them, as an indication that the approach has been whetted thoroughly.
- c. **Approach:** Support or pilot data available from prior research which helped build the hypothesis and objectives of the current proposal is described in this section. It is advisable to include statements on how existing data has shaped the approach to executing the project. The approach to the project must bridge the path between pilot data and project outcomes to assimilate into the objectives of the proposal. The information can be included in subsections as follows:

- ***Experimental approach:***

- i.* Include the critical features of the project which have not been described in other sections of the application such as the human subjects' protection section. This includes details of the rationale for the research hypothesis and trial design (e.g., pragmatic, randomized, open-label.). Ensure that the definitions used to describe trial design are consistent throughout the application
- ii.* Include details of the target population under study and any specific characteristics that influenced the selection of this study population. For example, describe the age of eligible participants, the primary inclusion characteristic and how this group is best suited to support the expected outcomes of the project objective. This is the primary inclusion criteria for a clinical trial: e.g., subjects > 30 years of age who have suffered a Myocardial Infarction within three months prior to screening.
- iii.* Include the research processes to be employed in the execution of the trial. This commonly includes a description of in-person clinic visits, phone contacts, medical chart reviews, questionnaires to be administered, psychological tests, lab tests and other procedures required in the trial. Any non-traditional study methods such as use of online applications should be described briefly.
- iv.* The clinical trial required for this FOA should follow Good Clinical Practices. Implementation of GCP concepts and monitoring of

compliance should be described briefly. The Human subjects' protection section will include additional details of this concept and the information between these sections should not overlap.

- *Supporting Data:* Pilot data or preliminary work accomplished by the PI or other researchers on the project topic should be described. Only relevant research studies that supported and influenced the development of the current proposal must be included. The NIH has a definition of clinical trials found here: <https://grants.nih.gov/policy/clinical-trials/definition.htm> . If the proposed project meets the definition of a Phase III Clinical Trial, information on the analysis of the primary objective and any subgroup analysis should be described. Note that details of biostatistical considerations will be included in a section specifically dedicated for this information on the application.

3.7. Statistical design and power.

This section has no page limit and is uploaded as a PDF document on the SF424 form. The outline for this section should be in place at the time of the NHLBI staff consultation meeting and modified based on feedback received at the meeting. The statistical design of the study determines the size of the project by influencing the sample size, project budget, and execution timeline. For multi-site projects, the sample size will help determine the number of sites required to complete the project on time. The statistical design and plan should include the following description:

- Computation of the required sample size and the assumptions made to arrive at this number, including the statistical power.

- Acceptable dropout rate to account for incomplete data, patients who withdraw or lost to follow-up before trial completion.
- Analysis plan for the study objectives: primary, secondary, tertiary, exploratory endpoints.
- Software and standard statistical methods to be used.
- Any interim analysis to be conducted and the time points in the project to achieve this, its possible outcome and the plan for action depending on interim analysis results or delays in reaching project milestones.
- If the interim analysis process and results will be blinded or if unblinded data will be used.
- Stopping rules for the clinical trial when certain thresholds are met.

The statistical analysis section will help develop the statistical analysis plan and the case report forms (CRF) when the project is funded. The CRF's are used by participating sites to collect and submit trial-related data. The statistical analysis plan is used by the biostatisticians and data management group to analyze data.

Given that the foundation of the project's success is based on the statistical plan, it is critical to get this section correct at the very beginning. Note that the statistical analysis plan should be described in a manner that independent statisticians are able to understand and replicate the plan. The NHLBI statisticians pay close attention to this section and often question why other approaches have been excluded. The study biostatistician should be able to explain the approach and justify the chosen plan.

Chapter 4. Administrative sections of the application

4.1. Cover Letter

A cover letter is to be included with the application and developed as follows:

Type the cover letter on the applicant institutional letterhead and address it to the NHLBI Division Chief from the PI. Include the following information on the letter

1. Title of application and FOA number
2. The name of the applicant institution and the PI's name and contact information
3. Statement if any component of the sub-award budget is not consistent in each year of funding, e.g., if a collaborator will only be compensated for three years of the five year project.
4. If the application has been approved for direct costs greater than \$500,000 in any given year of funding, include a statement regarding this approval and attach the NHLBI approval letter to the application.
5. If a video is to be submitted with the application, include this information on the cover letter. Failure to include this information can result in the video not being included in the review.
6. If the project will generate large scale human or non-human genomic data per the NIH Genomic data sharing policy, this should be mentioned in the cover letter.

A sample cover letter template is included in Appendix III.

4.2. Facilities and Resources

This section is written and uploaded as a PDF document and does not have a page limit. It should describe the facilities at the applicant institution in relation to project conduct. It is advisable to start with a brief history of the institution along with the central departments available to support the research project (SPA, clinical departments, research unit, and infrastructure). If the institution has prior experience administering federal grants with success and is recognized for its research accomplishments, it would be appropriate to include this information on this section. The section should include the following information:

- The PI should narrow down facilities available for the conduct of the project. For example, clinical trials can include how patients will be seen and resources available to screen and support patients throughout the trial. If medications are used, the availability of a dedicated and access restricted space or pharmacy to control the study product should be included.
- Office space with equipment such as computers, printers, fax capabilities, storage space for paper charts and online research records should be described.

The objective of this section is to inform the reviewers that the applicant institution has resources to support the project or has a plan to acquire necessary facilities if the project is funded. If resources are to be acquired, this section should describe a timeline for acquisition, and assure the reviewers that time will not be spent on establishing and fulfilling project needs instead of project execution once funding is released.

For multi-site projects, this FOA expects facilities and resources available at the various participating sites to be included in the application. The PI can obtain this information by drafting a template letter which is sent to all participating sites. Each site can customize the letter and include their site-specific resources available to support the project. Alternately, this information can be collected through a participating site survey. The survey includes questions related to the availability of facilities and resources relevant to the proposed project at each site. This survey is sent to all participating sites, and the responses are tabulated and included on the application under this section.

4.3. Equipment

This section is uploaded as a PDF file and does not have a page limit. It should include information about equipment already available for the project and those that will be purchased using project dollars. Office equipment such as computers and printers should not be listed here. List equipment specific to project conduct, e.g. freezer, pumps for intravenous medications, etc.

4.4. Senior Key Person profile and Biosketch:

The NIH has a specific biosketch format limited to five pages and is available at:

<https://grants.nih.gov/grants/forms/biosketch.htm>

A biosketch must be submitted for all Senior Key Personnel on the project. Senior key personnel are individuals that play a significant role and contribute to the scientific development and administrative execution of the project. For this FOA, a non-fellow NIH biosketch format must be used. Also note, the template has an ‘approved through’ date on the top right side of the page. Ensure that the template remains valid through the date of

the grant submission. In some instances, the NHLBI may release a notice stating that templates that are expiring in the year of the application are valid through certain submission cycles. The PI must pay attention to these details and request all key persons submit their biosketch on the correct template.

The template has four sections from A through D. Complete the key personnel name, including the eRA Commons username and position title on the first page and provide details of education with dates, degree obtained and the institution of granting the degree.

In **section A**, the key person should provide a personal statement. While this section can be used to outline significant accomplishments, since the overall biosketch is limited to five pages, section A should be used to describe the collaborator's previous work, their interests, and accomplishments in the research related to the proposed project. Only four citations from the key person's work relevant to the project can be included in this section. This section is often modified depending on the role of the key person and associated project when an NIH biosketch is required for any proposal.

Section B captures the positions and titles of the key person. They should be listed in chronologic order and formatted neatly for easy readability. Honors related to the area of the proposed project should be highlighted in this section.

Section C requires listing five of the key person's most current contributions to science. The scientific contributions that are related to the proposed project should take precedence. Writing a few sentences about each contribution and how it leads to the proposed area of grant submission is an excellent way to show continuity in one's

contributions to the specific topic. For each contribution, the biosketch allows up to four publications. If no significant contributions are to be included, the key person should list “NONE” under section C. Finally, a link to the complete list of the key person’s published work should be obtained from the NIH MyBibliography page and provided at the end of section C.

Section D requires the key person’s research support and ongoing funded projects to be listed. List the project title, years of funding support and the role of the key person for each project. List the most recent ongoing funded projects first followed by those that have been completed. The goal of this section to highlight the versatility and success of the key person in obtaining research funding, completing projects and validating for the NIH that there is no overlap in funding sources on the proposed project. A sample biosketch for the Principal Investigator has been included in Appendix IV.

4.5. Structure of the project team

This document is uploaded as a PDF attachment on the SF424 form and does not have a page limit. The information included here should describe how the entire project team is set up to drive the clinical trial towards success.

- It is advisable that the document begins with a graphical representation of the different positions held by the project management team (Appendix V). The representation should be a hierarchical flowchart which depicts the relationships between the various positions and ultimately reports up to the PI. Note that the representation should be simple and easy to follow but comprehensive to show the different groups that are working together on project execution.

- Following the graphical representation, the details of each position function and names of the individuals fulfilling those roles should be provided. Providing these details is indicative of the thoughtful planning and preparedness of the project team to initiate the grant as soon as it is funded. Reviewers do not like position descriptions be listed as to be determined (TBD) unless the position requirement is unique to the project and will be filled upon successful funding. The role of the EC and its members should be described in this section as well.
- The communication and coordination required between the different working groups such as project manager, biostatisticians, data management, the monitoring group, EC, and vendors should be clearly described.
- If the data coordinating center accompanying this cluster FOA is a separate entity, the relationship and coordination between the CCC and DCC should also be described.

Overall, a task grid outlining the processes overseen by each role on the PI's team is helpful for the reviewers in understanding project management and execution.

4.6. Recruitment of women and minorities

The NHLBI has been an advocate of ensuring women and minorities are adequately involved and represented as research participants so that project outcomes can be generalized to these populations, especially if it involves clinical outcomes. The PAR-18-407 requires the PI to describe concerted efforts planned to enroll these groups to include:

- Recruiting efforts to be implemented such as working with women's groups, or practices that focus on women's health and communications with outreach and support groups that work with minorities.
- The section should also include an estimate of women and minorities that are to be recruited in the study and if subgroup analysis or outcomes are expected to vary based on the proposed objectives. Pilot data on how the expected sample size related to the inclusion of women and minorities was derived should be included
- If certain groups such as from the vulnerable population, pregnant women or specific ethnic groups are to be excluded in the project, this should be disclosed with substantial justification.

4.7. Recruitment and retention plan

This section of the application is completed as a PDF document and uploaded on the SF424 form. It should describe the plan to recruit subjects in the clinical trial to meet the overall enrollment goals. Specifically, the plan should provide:

- A breakdown of planned enrollment by each year of funding should be included to help the reviewers envision the progress of the trial and when data for the evaluation of primary and secondary trial objectives and interim analysis will become available.
- Through the participating site survey (Appendix VI), the expected enrollment at each site per month and the expertise of individuals responsible for recruiting subjects, screening and consenting at these sites should be described. The FOA

requires a table of the sites identified to participate in the clinical trial with their commitment in terms of enrollments in each month of the study

- For special populations (e.g., rare disease proposals), women and minorities, the use of community or patient advocacy groups to assist with recruitment should be included. If vulnerable populations are included, a plan to protect their rights and welfare throughout participation is required.
- Primary and back up strategies, along with plans to evaluate study progress in terms of subject recruitment and retention should be described. For interventional clinical trials, the plan to obtain subject vital status especially for those who withdraw or drop out of the study prematurely should be in place.

4.8. Single IRB plan

To consolidate and streamline ethics review and reduce study start-up timelines, the NIH requires all non-exempt human subjects research multi-site applications submitted on or after January 18th, 2018 to identify a single central IRB which will provide oversight of the project and participating sites. This requirement is extended to the PAR-18-407 announcement and the plan to include a single IRB must be submitted as a PDF attachment and has no page limit. The PI must follow the steps noted below to identify a single IRB for its services and include details on the grant application.

- Early in the application development process, the PI should reach out to several central IRBs that can provide the required service. Details regarding the proposal, duration of the project, number of sites, number of subjects and estimated timelines should be provided to each IRB to allow them to evaluate if their services are appropriate for the project. The IRB will also provide an estimate of

costs for its services. The research team should obtain a cost breakdown for each year of funding.

- Some IRBs are willing to share a list of trial sites that accept their review which helps with evaluating the most feasible IRB to include on the project, based on the sites participating in the clinical trial.
- On the survey sent to sites for information on their facilities and resources, a question related to the acceptable central IRB review for the site should be included. These responses will also help in the decision of choosing the single IRB for the project.

Based on information received, the EC, PI and university SPA administrator must identify the single IRB of choice. A letter of support from the chosen IRB must be obtained stating their commitment to providing oversight to the project and noting their budget for each year of funding.

Additionally, this section must include details on how communications between the IRB and sites will be handled. These would include initial submissions, event reporting, deviation reporting, and annual renewals. A clear plan of implementing IRB decisions must be described to ensure sites remain in compliance with human subjects' protection. For sites that will work with the chosen IRB, information related to their willingness to execute a reliance agreement to accept the central IRB review for the project must be included. The actual reliance agreement should not be included in the grant submission and can be executed between the site and the central IRB once the project is funded. For sites that are unwilling or unable to accept the chosen IRB for oversight, an explanation must be provided with an alternate plan for oversight at these

trial locations. The NHLBI will evaluate if the justification provided is sufficient to exempt these sites and allow a different IRB to review the project at these sites.

4.9. Data and Safety Monitoring Plan

The PAR-18-407 FOA requires the conduct of a clinical trial and human subjects enrolled in the trial must be protected adequately. Plans to oversee subject protection through the evaluation of data and defined safety parameters are outlined in this section and submitted as a PDF document uploaded on the SF424 form. The NIH requires a Data Safety Monitoring Plan (DSMP) commiserate with the risks, size, and complexity of the trial to be included as well.

- This section should define the expected adverse events from trial participation and how they will be evaluated, recorded, reported and analyzed. The process to train site staff on identifying events and the reporting pathway should be described
- Once the site reports events, the process for the project team to review and evaluate these events and track trends must be described.
- Include what data points will be monitored from a safety standpoint.
- Depending on the size of the trial, a Data Safety Monitoring Board (DSMB) will be constituted upon successful funding and in collaboration with the NHLBI.

This Board will consist of independent physicians, biostatisticians, and experts in the field of the proposed project. The NIH will appoint members of the Board; however, this plan must describe the composition of the board as proposed by the PI without naming specific individuals.

- The frequency of the board meetings including data they will review, the format of meetings and data review (online versus in person and blinded versus unblinded data) must be included. Stopping rules depending on event rates or from meeting pre-defined thresholds should be described briefly to show thought has been given to protecting subject safety. The DSMB will decide the final stopping rules and acceptable safety thresholds which will be incorporated in the Committee DSMB and incorporated in their charter at the beginning of the project
- The PI and EC will enforce the DSMB's decision on trial modifications and stopping rules. It is important to mention in this section that the DSMB will function independently and members will not have a conflict of interest with study conduct.

4.10. Letters of support

Letters of support must be included from the following individuals and groups:

1. **Key stakeholders such as members of the EC:** The letter should be addressed to the NLHBI Division Chief and outline the individual's support to the project, their time commitment and the specific role played by the EC member on the project. If an EC member bills a consulting fee for their role on the project (i.e., not salaried through sub-award paperwork), they should mention their time commitment and hourly rate on the support letter.
2. **The PI's institutional department chair or applicant institution administrators:** The College Dean, Department Chair and other official university administrators should also provide a support letter if possible. This

letter will state that the applicant institution is aware of the scope of the project, has evaluated its ability to provide the required resources and is willing to support the project if funded.

3. **Vendors:** Vendors supporting the project such as the Central IRB should also provide a letter of support along with their budget information and clearly stating their role and capabilities in supporting the project.
4. **Individual site Principal Investigators or institutions:** the PI at each site on the multi-site clinical trial should provide a letter of support stating that they have evaluated the project, the inclusion/exclusion criteria for patients, reviewed their patient population and resources, and are confident of successfully participating in the trial if funded. Each site support letter should also include an approximate number of patients the site can enroll each month. It would be useful to note how each site arrived at this contributory number to assure the reviewers that the commitment is realistic. Common examples include monthly enrollment estimates obtained through medical chart review or the number patients seen at the site recently with the condition under study.
5. **Consultants:** It is advisable to collect a letter of support from the consultant outlining their experience to contribute to the project and clearly stating their time commitment and hourly billable rate

It is advisable for the PI to draft letters of support templates and send those to the participating sites along with the survey, asking them to place the language on institutional letterhead, enter site-specific details, and sign and return the letter to the PI. This approach is successful when compared to asking sites to write their support letter for

the project. Note that the process to obtain support letters from all participating sites can take a few weeks and should be done in parallel with other application processes. A sample letter of support template has been included in Appendix VII of the manual.

4.11. Data dissemination plan/Resource sharing plan

Since the NHLBI is a federal agency supporting the PAR-18-407 announcement through taxpayer dollars, it is crucial that the outcome of the research project is made available to the general public as well as researchers worldwide. The data enables other researchers to build on the project idea and explore it further, develop alternate hypotheses or serve as pilot data for subsequent projects. For projects with direct costs greater than \$500,000 in any given year of funding, the NIH expects its Data Sharing Policy will be followed. These guidelines can be found at https://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm. These guidelines must be carefully reviewed and incorporated into this section of the PAR-18-407 application.

The NIH expects that data used in the analysis of the project objectives will be made available to other researchers. This requirement goes beyond the sharing of aggregate data. Protected health information should be removed from any datasets before being shared. The project EC should discuss the timeline for data release along with the data formats to be made available. Data should be available for sharing before the primary findings are published. The project team can propose to release the required dataset in different formats such as de-identified data by geographic location, gender-based data, and dataset with limited identifiers. The process for requesting datasets must

also be described to include the need for any agreements to be executed before a requestor is granted access to the study data.

4.12. Study timelines

This section is written and uploaded as a PDF document on the SF424 form and has no page limit. The section should begin with a description of the overall timeline of project execution from funding to final study close-out and publication. It should provide a breakdown of the important milestones to be achieved in each year of funding. This FOA is divided into a UG3 and UH3 phase. The UG3 phase covers the first year of funding. The FOA has specific requirements that must be met in this first year/UG3 phase before the NHLBI will consider funding the remainder of the project. This approach has become prevalent with the NIH in recent years to mitigate the risk of projects failing to meet their primary goals or requesting project extensions and additional funding beyond what was initially approved. For the PAR 18-407 announcement, the NHLBI expects the following processes to be completed in year 1 or the UG3 phase of funding:

- Documents such as the study protocol, informed consent form, data management and dissemination plan, communication plan, project management plan, and site performance plan should be finalized.
- DSMB committee and charter finalized
- Finalization of contracts and third-party agreements
- EDC and data collection tools completed and in production.
- Site training plan and its implementation at sites that have been activated

- Completion of regulatory approvals (FDA, IRB)
- 25% of planned sites must be activated
- One participant must be enrolled in the clinical trial before the end of year 1

At the end of the UG3 phase, an evaluation meeting will take place between the PI and the NHLBI Program Official and if the milestones have been met satisfactorily, a UG3-UH3 transition discussion will be completed. This will allow the project to continue through the remaining years of funding.

For the remaining years of funding, this section should specifically address the number of patients to be enrolled in the trial and the timing of other key events such as DSMB meetings, investigator study meetings and data analysis. In the final year of funding, the site timeline should include the process of data cleaning and analysis, timely closure of study sites, data sharing and dissemination time points, publication and presentation of study results and final close-out of the project with the NHLBI.

At the end of this section, the study timeline should be presented in table format. This visual representation of the entire timeline noting key milestones is beneficial for reviewers to gauge the planned progress of the study in each year and identify any challenges that could stall project completion. An example of this table is included in Appendix VIII of the manual.

Chapter 5. Budget Development

5.1. Budget components

The NIH has two types of budget forms, and the correct form must be utilized based on the overall project budget. For projects that utilize greater than \$250,000 in direct costs in any year of funding, an R&R Budget template is required. For projects less than \$250,000 in direct costs per year of funding, a modular budget format is required. If the PI completed a staff consultation meeting and obtained an NHLBI acceptance letter, this would qualify for the R&R budget template, as the expected direct cost in any given year of funding is \$500,000 or more.

The total budget in direct costs should be within or precisely at the costs proposed to the NHLBI in the letter of intent and recorded on the acceptance letter. This letter will state the budget cap set for direct costs in year one of the project and the total budget cap for the project. The PI must ensure that neither of these budget caps is exceeded. For direct cost that is over the year one limit or total project budget, the NIH Program Officer should be consulted. This may require reinitiating the project application and staff consultation meeting and will add to the submission timeline.

The budget should be built on an excel template and shared with the SPA administrator for review and for the addition of indirect costs (Appendix IX). Note that budget building is time-consuming, especially since the acceptance letter from the NHLBI will include the final approved budget cap for the study and there is no room to negotiate outside these approved numbers at the application stage. Budget negotiations may be permitted once the project is funded and the NHLBI accounting and agency

finance staff get involved in funding allocations. At this stage too, the room for negotiation remains marginal and may require strong justification with several rounds of discussion that could affect the project timelines.

The budget requires the listing of line item costs under each category of expense, e.g., salaries, equipment, supplies, vendors, and sub-awards. A list of allowable costs and activities which can be billed to the grant can be found at:

https://grants.nih.gov/grants/policy/nihgps/html5/section_7/7.9_allowability_of_costs_activities.htm .

Note that a budget justification page is also required as part of the application packet. Therefore, it is wise to incorporate details of each line item cost and associated rationale on the excel spreadsheet to help create the justification document and for reference in the future.

Salaries: The research team should gather the actual costs of salaries and fringe benefits for project personnel. For individuals at the applicant institution, human resources may be able to provide this information. Salaries should not be inflated for cost of living or promotions/raises. They should be stated at base salary plus fringe and benefits at the time of the application. The NHLBI recognizes that the cost of living raises will be requested if the project is funded. For individuals with salary support requested through the grant, a time commitment for each year should be included to justify the costs. Time commitment can vary in each year of funding and salary support must equate to the person's contribution.

The NIH places a salary cap in each fiscal year for all personnel included in the grant application. This cap is decided by the federal government and payment of salary for any individual being paid from the grant cannot exceed the Federal Executive Level II pay scale. The cap for fiscal year 2019 is set at \$189,600. Individuals and collaborators budgeted on the grant who fall under the Executive Level II pay scale can obtain salary support to include base salary, fringe and benefits of up to \$189,600 per year. If the individual's salary is above this pay scale, the remainder of their salary must come from sources other than the grant. The PI must contact the institution SPA administrator for assistance with budgeting salary using the NIH cap for applicable individuals in each funding year of the grant.

Using the definition of key personnel from section 4.4 of this manual, PI should determine which key person on the project will be budgeted to the grant and if the NIH salary cap is applicable to them. Salaries for key persons are listed on section A of the R&R budget form of the SF424 form. Note that it is not mandatory for key persons to be paid through the grant. For those key persons that do not require salary support from this grant, the PI should include a justification indicating the key person's role and commitment to the project despite being paid through non-grant sources.

For non-key persons such as research coordinators, pharmacist or administrative assistants who will be budgeted to the grant, obtain their base salary and fringe plus benefits and include these under section B of the R&R budget form.

Consultants: For consultants, the total expense per year must be listed. It is advisable to collect a letter of support from the consultant outlining their experience to contribute to the project and clearly stating their time commitment and hourly billable rate. Note that a

strong justification for bringing consultants on board is required both by the NHLBI and almost always by the applicant institution. Consultants can be more expensive than salaried employees depending on their time commitment to the project, and therefore the justification to include them must be strong and clearly stated. Consultant fees are listed as a separate line item in section F of the R&R budget form.

Sub-awards: Sub-awards must be detailed and itemized in terms of budgetary allocations and scope of work. Each sub-award must be listed separately with all the required information. Note that some academic institutions that provide services or collaborate on such large grants have their process of generating sub-award paperwork. It is advisable to initiate this process early, so all paperwork, approvals, and signatures are in place before the application deadline. Sub-award costs are listed under section F of the R&R budget form.

Equipment: The NIH considers tangible property or equipment with a useful life of more than one year and cost of greater than \$5000 per unit as equipment. Costs associated with purchasing project equipment must be itemized and listed through each year of funding in section C of the R&R budget form. The justification will explain any calculations, use of equipment via lease or purchase and duration of equipment use. Any maintenance contracts will also be included in this cost.

Travel expenses: Travel associated with administering the grant can be budgeted to the project. The PI should expect to travel to the NHLBI at least twice in year one of funding and once every year after that. In the first year, the PI and additional key personnel or the project manager will travel to the NHLBI to review the project and participate in a kick-off meeting. Per the FOA, the project must achieve certain milestones by the end of year

one of funding when the NHLBI will evaluate progress and decide if the rest of the project should be funded. In subsequent years, meetings with the NHLBI staff can take place via conference calls, at national meetings or the NHLBI office. During the clinical trial, it is imperative to conduct study site visits at a few study locations. Travel costs for these visits must be calculated.

The PI will also need to budget travel to national meetings to present study findings during the project and once the project analysis is completed. Travel costs and registration for national meetings must be included. To compute travel costs is advisable to use the published government per diem rates for the year of application for items such as airfare, mileage, hotel, food, and miscellaneous and incidental expenses. Using per diem rates make it easy to justify the cost of each trip and reassure the NHLBI that project dollars are not spent on expensive travel related to the study. Travel costs in each year are listed under section D of the R&R form.

Supplies: Materials and supplies required for project execution are calculated to their best estimates. These are items that will be used to execute the project and can include items such as office supplies or lab reagents. For multi-site studies, for example, the applicant institution will provide regulatory binders to file study regulatory documents. Cost of each office supply item can be obtained from an online store and used to calculate the overall expenses related to this category. Computers can be listed under this category and billed to the grant if it will be used solely in the execution of the grant. The supply requirement and calculation of costs should be included in the budget justification document. The cost for supplies is listed under section F of the R&R form.

Site-specific expenses: Since this FOA applies to multi-site projects, reimbursement to the sites must be computed and included in the budget under section F of the R&R form. For clinical trials, sites can be reimbursed by per patient enrolled, a flat rate for screen fail subjects and other administrative costs such as report preparation and regulatory paperwork completion. These costs should be calculated by region (e.g., the US, Asia) and allocated to each year of the project budget. An explanation of how these costs were calculated is to be included on the budget justification page.

IRB/Ethics Committee costs: The NIH has recently moved towards the requirement of multi-site projects needing to use a Central IRB for ethics oversight. This requirement extends to the chosen NHLBI announcement as well. In consultation with the applicant university, the PI should discuss which single IRB will provide ethics oversight of sites in the project. Note that if several countries are included on the project, the ethics committee requirements may vary based on regulations and the applicant university Human Subjects Protection Office may be able to guide in this regard. For sites within the US, several central IRB (CIRB) offer services and are prepared to work within the NIH expectations. The chosen CIRB can provide a letter of support outlining their services and accomplishments as well as their commitment to support the project if funded, along with a budget estimate. Including this letter in the submission indicates to the reviewers that preliminary work has been done and no additional time will be expended in getting project processes in place if the application is funded. The budget justification should include an explanation of IRB costs in each year of funding and the reviews the cost will cover such as the number of deviations, the number of expected events and the initial and annual submission at each site.

Site specific expenses and IRB costs can be grouped together and listed as other costs under section F of the R&R budget.

Institutional Indirect costs: Once all direct costs are added, the PI should send the excel spreadsheet to the SPA administrator assigned to the project at the applicant university. This individual will review all line item costs for accuracy. If unallowable items are included, a discussion between the SPA administrator and PI should be arranged and corrections or substitutions made. Once finalized, the SPA will include the institutional indirect costs based on the Facilities and Administration (F&A) rate negotiated with the Department of Health and Human Services for federal grants. F&A costs typically cover institution SPA administrative costs to support the grant submission (pre-award) and activities in project execution (post-award) such as annual reporting, billing, compliance and oversight. Note that the indirect costs for the applicant institution are not included on the NHLBI acceptance letter.

For sub-awards, the paperwork must include the sub-award institution F&A costs as well. To prevent duplicate billing of indirect costs, the applicant institution can charge its F&A costs only on the first \$25,000 of the sub-award budget. This is to cover the applicant institutions efforts in administering the sub-award.

5.2. Budget justification

This is provided as a PDF attachment and uploaded on the budget sheet of the SF424 application. Each item with a cost listed on the project budget must be included on this document with an associated justification. Salary for each individual should be explained along with their role and time commitment. Supply requests, travel and

consultant fees can be described and explained further in this section. Finally, the applicant institution's indirect costs rate can be included in the justification so that reviewers understand how the dollar amounts were computed.

Chapter 6. Human subjects' protection

Clinical Trials involving human subjects must describe the plan to include the appropriate population through robust screening. The plan should also include steps to protect participants per the International Conference of Harmonization and Good Clinical Practice guidelines.

The human subjects' protection plan is written in four sections and uploaded as a PDF document. The section has no page limit and should be compiled as follows:

- A. Risks to Human Subjects
- B. Adequacy of Protection Against Risks
- C. Potential Benefits of the research to participants and others
- D. Importance of Knowledge to be gained.

6.1. Risks to human subjects

- i. *Human subjects' involvement, characteristics, and design:* This section begins with a brief description of the overall study design. Key-words such as randomized, double-blind, placebo-controlled should be included in the design description. The description sets the stage for the level of risks associated with the project, and this section must address how those risks will be identified, mitigated and controlled. This section should also describe the population under study. The clinical trial inclusion and exclusion criteria against which participants will be screened for study inclusion must be specified in detail. If there is more than one study intervention, these will be included here, and the method to assign each participant to a study intervention will be described

(e.g., randomized). Include the numbers of participants to be enrolled in each study intervention arm. Since the PAR-18-407 announcement involves a multi-site clinical trial, the role of participating sites in human subjects' research should be described along with the contributions of participating collaborators.

- ii. *Study procedures, materials, and potential risks:* Details of all procedures to be conducted as part of the clinical trial will be included in this section. This includes visits to the study site by patients, procedures to be conducted at each visit (such as blood draws, questionnaires, obtaining medical history, and assessing adverse events) and data collection methods must be described. Include here, if protected health information (PHI) or identifiable information will be collected as part of the project and the process to ensure limited access and prevent a breach of confidentiality. The section should describe the known risks for each procedure and data collected. This could include risks of blood draws, discomfort in completing responses to questionnaires and risk to data safety from breach or loss of data. The section should be thorough and indicative that the PI and EC have evaluated risks associated with patient participation and has a plan to mitigate them appropriately. Typically risks in a clinical trial should be evaluated as physical, psychological, social, cultural, financial and legal risks.

If alternative methods are available to help arrive at the same research outcome, those should be included with an explanation of why those methods are not being utilized or reserved as back-up strategies.

6.2. Adequacy of Protection against Risks

- i. *Informed consent and assent:* The informed consent process to be utilized on the clinical trial should be described. Information on the circumstances under which consent will be obtained should be included. The contents of the written informed consent and the process of documenting the consent should be included. If patients with an altered decision-making capacity or vulnerable patients are to be included, this should be described along with a plan to protect the rights and welfare of this population and all participants in the trial. If the use of a legally authorized representative or witness to the consent process will be allowed, circumstances for these should be described. If a waiver of some or all elements of consent will be obtained from the IRB, justification for the same should be noted. This FOA allows a sample informed consent form to be included as an appendix to the application. The research team should ensure the consent form submitted is written to include all essential elements as described by the Department of Health and Human Services, Office for Human Research Protections.
- ii. *Protection against:* The plans to protect, minimize and mitigate risks described above should be described in this section. This section should also include plans to protect data collected as part of the project, included PHI and identifiable information. Include who will have access to the data collected on the study and how this will be tracked. Where applicable, emergency intervention such as medical treatment to be provided or recommended should

be included. The process of emergency unblinding if applicable must also be included in this section.

- iii. *Vulnerable subjects*: The inclusion of vulnerable population in the clinical trial should be described here with justification for their inclusion. These would typically involve fetuses, pregnant women, children, prisoners, institutionalized individuals or others who could be considered vulnerable.

6.3. Potential Benefits of the research to participants and others

This section should describe the potential benefits of the research to participants and others and the knowledge to be gained from the project outcome. Benefits should not be overstated. The section must include how the risks are reasonable compared to the potential benefits (risk-benefit ratio) of participation and the knowledge to be gained. The information included should not state the compensation offered to patients as a benefit of participation in the trial.

6.4. Importance of knowledge to be gained

The human subjects' protection section should end with information on why the risks and processes undertaken are appropriate when compared to the knowledge to be gained from the project. If there are alternate research options available, their feasibility in comparison to the chosen design must be explained.

Chapter 7. Submission process

7.1. Submission to the applicant university SPA

The PI is notified of the applicant university's internal submission deadline required to review the entire application before it is officially submitted to the NHLBI. All stakeholders must be aware of this deadline and make every effort to meet the timeline. Note that SPA administrators are assigned to work on several projects with the same submission deadline and project review can compete for their time and attention. The sooner the sections of the application are submitted for internal review; a more comprehensive and committed review can be completed by the assigned SPA administrator. These individuals are highly experienced with grant submissions and have a keen eye in identifying issues and discrepancies, and therefore, it is recommended that applicants utilize this facility judiciously. Applications that do not clear the internal institutional review process are most often not submitted officially to the NHLBI and can create tensions between the PI and institutional officials.

It is recommended that once the budget and study justification is prepared, it is sent to the assigned university SPA administrator for review. This area of the application most often brings up surprises and needs several rounds of modifications before the budget is finalized. The budget justification is also revised to match any updates made to the budget numbers.

As other documents related to the administrative sections of the application are completed, it is advisable to send them to the SPA administrator for review. Often the administrator will begin the official application in the system and upload the attachments

provided; to check for basic errors such as exceeded page limits and formatting issues. Errors from the system can help the PI revise the documents appropriately. Review of these documents by the SPA administrator also ensures that commitments made on project are realistic and within the achievable scope of the university.

The university administrator may request the scientific sections to be submitted for internal review, a few days before the official submission deadline. SPA administrators routinely peruse these documents for formatting, grammatical errors and to confirm page limits are met. If they find contradictory information on the write-up, they may inquire with the PI.

Once all changes are made, the SPA administrators will complete the official application online and attach all documents provided. They will share a copy of the draft application with the PI's team. It is crucial that the PI, members of the EC and project manager review the draft application in detail to confirm all information is in order. At this point, the PI's team should be reviewing all sections and information input on the application, including the fillable PDF sections completed by the administrator. Inconsistencies should be corrected, and the application reviewed multiple times until an error-free version is acceptable to all. This results in a final application version ready for official submission.

7.2. Application submission through the grants portal.

Once the final clean version is ready for submission and uploaded into www.grants.gov, the Authorized Official at the applicant university will sign the final application and complete the submission process through the federal grants submission

portal. Note that the submitted application is time stamped by the system to include the date and time of portal submission in the applicant institution's local time zone. For the PAR 18-407, the application must be submitted by 5 pm local time by the date noted on the application. An application submitted after this deadline is rejected by the system and will not proceed to NHLBI review. The Program Officer and staff at the NHLBI do not have the authority to override this requirement or grant exemptions to late submissions unless there is a technical issue with the federal grants submission portal. In such cases, a discussion would ensue with NHLBI officials and does not always result in obtaining permission to submit after the deadline. To avoid delays and provide time to circumvent submission challenges, the NHLBI encourages applications to be uploaded and submitted a few days before the official deadline.

Upon successful submission, the university official and PI receive an automated message noting the application was successfully submitted. The message includes the details of the submission. It also contains a note if warnings have been identified on the submission and instructions to access the application through eRA Commons to view the warnings. The instructions note that the institution has two business days retracted for corrections and a new application is uploaded, it overwrites the previous submission and allocates a new date/time-stamp of the application uploaded. If this time-stamp is after the official submission deadline, the application may get rejected. It is advisable in this scenario, to contact the NHLBI Program Officer and seek guidance on how to address and resubmit corrected applications. Changes to the application have to be routed through the applicant university signing official again.

7.3. Scientific Review and feedback

The applicant university or PI can be determined the status of the application through the eRA Commons account. When the status of the application is updated by the Scientific Review Officer (SRO), an e-mail notification is sent to the PI alerting him to a new status being available through eRA Commons.. The first status update is received a few weeks after the submission when the SRO has had a chance to review the submission for completeness. An update stating that the application has been received and will be assigned to a review committee is indicative that the submission is moving into the next stage of review. If there are missing documents, the e-mail would state the submission has been denied and include the reasons for the same.

In subsequent weeks, an additional update is provided when the application is assigned to a scientific review committee and their meeting date has been finalized. The notification also states that the committee roster will be available approximately thirty days before the meeting date. The PI can log into eRA Commons and view this roster once available. Per NHLBI policy and as stated on the roster, the PI should not contact any of the committee members directly to discuss the application. Breach of this policy can result in the application being withdrawn from review and disqualified from future submissions.

Between the official submission and up to 30 days before the Scientific Review Committee, any new information such as publications that could affect the design or outcome of the study or assist with scientific review can be submitted to the Scientific Review Officer to include in the review packet. Only relevant information should be submitted in these instances.

Following the Scientific Review Meeting and in approximately five business days, the raw score assigned to the application is uploaded into the eRA Commons account and is available to the PI and applicant university. Depending on the scores, the PI should reach out to the NHLBI Program Officer to discuss the review meeting and chances of funding. The application is scheduled to undergo Advisory Council review in eight weeks before the final decision for funding is announced. While there is not much the PI can do at this stage but wait for the final outcome, the Program Officer can share the application's chance of success depending on the applications reviewed and general scoring assigned at the scientific review meeting. Approximately thirty days after the meeting, the summary statement noting reviewer comments is uploaded into the eRA Commons account. The PI and EC should access a copy of this statement and carefully review the feedback noted. If the comments appear to be indicative of an incomplete or inconsistent review, then the Program Officer should be contacted to express concerns and to determine the next steps.

For projects that do not get funded, a resubmission may be possible. The Program Officer can provide guidance on the process to be followed. It should be noted here that a resubmission is assigned an alphabetic code indicating to the reviewers that the submission has been updated and resubmitted. It is strongly recommended that reviewer comments from the first round be addressed on the resubmission. If a recommendation made by a reviewer is not accepted, the resubmission application should justify the same. If changes are made in response to reviewer comments, the PI and EC should ensure the entire application continues to flow logically and the budget remains unaffected. Reviewers assigned to a resubmitted application may differ from the initial set of

reviewers. They perform reviews with a fresh set of eyes while also noting responses and changes made to previous critiques.

The process to resubmit the application is as extensive as the original submission. Care should be taken to confirm that the FOA number or requirements have not changed. Efficient planning to submit a revised and stronger proposal should be done as there are limitations on the number of attempts for resubmission. Involving the Program Officer in every step is therefore crucial and will help set the team up for success.

Chapter 8. Conclusion.

This manual is intended to be a useful tool in assisting and providing the PI and associate research team members with a roadmap to completing a strong and review worthy application in response to the PAR-18-407 announcement. The effectiveness of this manual is enhanced when the PI and the associated team members take steps to understand their project and the submission requirements. A successful submission must involve careful planning, the interaction between team members and the need to be organized and systematic throughout the application process.

Following this manual and referencing it routinely during the application development period will allow the PI to strategize the inclusion and placement of content, assign the development of application sections to team members, administrators within the sponsored program office, and collaborators.

Please refer to the appendices for sample templates of documents used in the PAR-18-407 submission as noted in the respective sections of this manual.

The grant writing and submission process is challenging, arduous, and stressful. An unwavering passion for research with a commitment to succeed must remain at the forefront of the application process. The author of the manual wishes all applicants success in their pursuit of federal funding through the PAR-18-407 NHLBI announcement.

Appendix 1. NIH checklist

*checklist does not replace the solicitation. Please review program specific solicitation for compliance and completeness.

DUE DATE AND AWARD INFORMATION	
Internal applicant university deadline	XXX days prior to NHLBI submission deadline Internal submission due date: The following will be the minimal information required to meet the Internal SPA deadline 1. Working Title of proposal 2. Key Personnel, their roles and effort 3. Budget and Budget Justification 4. Information on whether animal and human subjects will be part of this research 5. Award length (how many years the grant will be awarded for) 6. Any subcontracts? With who? 7. Any keywords associated with your grant proposal
Award notification	At least 6 months after grant submission due date
LOI due date	30 days prior to application due date
Targeted application due date	5:00PM local time on DD/MMM/YYYY Scientific Committee review in MMM/YYYY Advisory council review MMM/YYYY Earliest start date of funding MMM/YYYY For application requesting \$500,000 or more in direct costs, contact the Program Officer for discussion and staff consultation.

FORMATTING INSTRUCTIONS	
Document format	PDF only; no headers or footers
Font type/size	Arial, Georgia, Helvetica, Palatino Linotype 11 or larger (smaller txt in figures, graphs charts is acceptable as long as

	they are legible when page view if 100%) Black font color
Line spacing	No more than 6 lines of type within a vertical space of 1 inch No more than 15 characters per linear inch (including characters and spaces)
Page size	8.5 x 11
Margins	0.5" all sides
Guidelines	<p>Announcement: CCC application 18-407 https://grants.nih.gov/grants/guide/pa-files/PAR-18-407.html</p> <p>DCC application 18-410 https://grants.nih.gov/grants/guide/pa-files/PAR-18-410.html</p> <p>SF 424 R&R application guide for research: https://grants.nih.gov/grants/how-to-apply-application-guide/forms-e/research-forms-e.pdf</p>

PROPOSAL DOCUMENTS			
	Assigned to	Documents:	Status
1.		Letter of Intent (30 days prior to submission deadline)	
		<ul style="list-style-type: none"> • Descriptive title • Name/address/telephone number of proposed PI • Names of other key personnel • Participating institutions • Number and title of FOA <p>Send letter to:</p> <p>Director, Office of Scientific Review National Heart, Lung, and Blood Institute</p>	

		<p>National Institutes of Health 6701 Rockledge Drive, Room 7214 Bethesda, MD 20892-7924 (Express Mail Zip: 20817) Telephone: 301-435-0270 Email: NHLBIChiefReviewBranch@nhlbi.nih.gov</p>	
1		Cover Letter Attachment: PDF attachment/no page limit	
		<p>The following collaborative information is required in the Cover Letter as one PDF file:</p> <ul style="list-style-type: none"> • The PD/PI(s) name(s), • Title of FOA • The Title (including the tag, e.g., “1/3”) • The Applicant Institution. Each site should submit an identical listing. • Statement that agency approval for >\$500,000 is included • Statement if proposed study will generate large-scale human or non-human genomic data <p>Note: If the direct costs of the combined CCC and DCC budgets equal or exceed \$500,000 in any given year, a copy of the NHLBI approval letter must be attached.</p>	
2.		Descriptive Title of Applicant's Project: PDF attachment/ Limit to 200 characters	
		<p>To allow NHLBI to identify a group of applications as a related set of collaborative applications, the titles for each application in the set must have the following format:</p> <ul style="list-style-type: none"> • A “1/N” indicator + Identical Title (e.g., “1/3”, where the 1/3 means this is site 1 of 3 sites in the set. The other sites will be labeled 2/3, etc.) • Titles may not exceed 200 characters in length, including the tag, e.g., 1/3, at the beginning of the title. 	
3		Project Summary/Abstract <input type="checkbox"/> - PDF attachment/No longer than 30 lines of text	
		<ul style="list-style-type: none"> • State the application’s broad, long-term objectives and specific aims, referring to the health relatedness of the project/ relevance of mission of agency. • Describe the research design and method of achieving goals 	

4	<input type="checkbox"/>	Project Narrative – PDF attachment/No more than three sentences	
		<ul style="list-style-type: none"> Describe the relevance of this research to public health 	
5	<input type="checkbox"/>	Bibliography & References Cited – PDF attachment/No page limit	
		<ul style="list-style-type: none"> Each reference must include the names of all authors (in the same sequence in which they appear in the publication), the article and journal title, book title, volume number, page numbers, and year of publication. When citing articles that fall under the <u>Public Access Policy</u>, were authored or co-authored by the applicant and arose from NIH support, provide the NIH Manuscript Submission reference number (e.g., NIHMS97531) or the PubMed Central (PMC) reference number (e.g., PMCID234567) for each article. If the PMCID is not yet available because the Journal submits articles directly to PMC on behalf of their authors, indicate “PMC Journal – In Process.” <p>For interim research products follow: https://grants.nih.gov/grants/interim_product_faqs.htm</p>	
6	<input type="checkbox"/>	Facilities & Other Resources – PDF attachment/No page limit	
		<ul style="list-style-type: none"> Describe how the scientific environment in which research will be done contributes to probability of success (institutional support, physical resources, intellectual rapport). Describe how the proposed study will benefit from the unique features of the scientific environment or from unique subject populations. Describe resources available at each site for multiple performance sites (obtain information from site survey) 	
7	<input type="checkbox"/>	Equipment – PDF attachment/No page limit	
		<ul style="list-style-type: none"> List major items of equipment already available for this project and, if appropriate identify location and pertinent capabilities. 	
8	<input type="checkbox"/>	Senior Key Personnel/Biographical Sketch - Limited to 5 pages per person on NIH Biosketch template	

		<ul style="list-style-type: none"> • Use NIH biosketch format - https://grants.nih.gov/grants/forms/biosketch.htm • Must Include eRA Commons User Name. • Applications should include only its own personnel and respective biographical sketches. • List Key personnel for CCC ONLY. • All Key Personnel who are major contributors to the study must provide an NIH Biosketch whether or not they are budgeted. • The PI (or multiple PIs) for the CCC cannot be Key Personnel on the DCC application. • The PI(s) of the clinical trial must be experienced in the conduct of multi-center clinical trial coordination and management, including success in meeting milestones and timelines, and have expertise in the content area of the proposed clinical trial. The experience of each PI and all Key Personnel must be carefully documented and roles and responsibilities must be well defined. In addition, the responsibilities and authority of each PI must be specified. 	
9	<input type="checkbox"/>	Specific Aims – PDF attachment/Limited to one page	
		<ul style="list-style-type: none"> • State concisely the goals of the research and summarize the expected outcome(s), including the impact that the results of the proposed research will exert on the research field(s) involved. • List succinctly, the specific objectives of the proposed research (to test the stated hypothesis, solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in a field etc) 	
10		Research Strategy – PDF attachment/12 page limit	

		<ul style="list-style-type: none"> • The Research Strategy must present an overview of the state of the science, status and relevance of the trial, a detailed discussion of the specific protocol, and the approach to data collection. It should include a brief description of study research objectives. <p>Significance (per FOA)</p> <ul style="list-style-type: none"> • Explain the importance of the proposed clinical trial and importance of the question must be clearly stated. • Explain how the proposed project will test the proposed hypotheses and why there is clinical equipoise. • Application should make clearly the need and timeliness of the study with emphasis on how the results will address an evidence gap and advance knowledge of theory and practice areas. Include a description of how the results will impact clinical care to improve health • Include a discussion on the costs and benefits of the study elated to trial significance <p>Innovation</p> <ul style="list-style-type: none"> • Explain how the application challenges and seeks to shift current research or clinical practice paradigms. <p>Approach</p> <ul style="list-style-type: none"> • This section should include a description of the supporting data, the experimental approach <p>a. Experimental Approach</p> <p>Describe critical features of the trial that are not already described in the PHS Human subjects clinical trials information to include the following:</p> <ul style="list-style-type: none"> ○ A detailed description and rationale for research hypothesis and rational for specific design chosen (pragmatic, randomized, unblinded etc). ○ A detailed description of the study population and why it is the most appropriate group to answer the question. ○ Detailed description and justification of all assessments such as clinical, lab, pt centered, behavioral, physiological and other outcomes addressing primary and secondary research questions. Use of pt reported outcomes as well as non- 	
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		<p>traditional data collection methods (telephone, mobile, web-based systems etc)</p> <ul style="list-style-type: none"> ○ Implementation and monitoring of GCP ○ Discussion of potential challenges in implementing the research protocol and how they will be addressed. Contingency plans if the effect size or event rate is underestimated. ○ Participant f/u procedures <p>b. Supporting Data:</p> <ul style="list-style-type: none"> ○ Describe the formative clinical studies (including any pilot studies) that are the basis for the proposed clinical trial. Include other research as appropriate to demonstrate that the approach chosen is justified. ○ If the clinical trial is Phase III, include relevant data used to determine that the proposed trial includes adequate numbers of subgroups of participants to allow for separate and adequately powered analyses. ○ For Phase III trials, include relevant data used to propose the adequate number of subgroups for a separate and adequately powered analysis. 	
11		Letters of support: PDF attachment/No page limit	
		<ul style="list-style-type: none"> • Letters of support from clinicians or clinical department chairs whose support are necessary to the successful conduct of the trial should be provided. • If parts of the costs of the trial are to be provided by sources other than NHLBI, provide Letter(s) of Support signed by an authorized representative. 	
12			
		<ul style="list-style-type: none"> • Data sharing Plan: Brief 1 paragraph description of how final research data will be shared or 	

		<p>sharing is not possible.</p> <ul style="list-style-type: none"> • Include a Data Sharing Plan with schedule for data sharing, format of final data set, documentation to be provided, analytical tools to be provided, if any, need for data sharing agreement, mode of data sharing. • Data sharing tips: https://grants.nih.gov/grants/policy/data_sharing/data_sharing_workbook.pdf 	
13		Appendix	
		<ul style="list-style-type: none"> • FOA PAR-18-407 allows only the consent form as an appendix 	
14		Inclusion of women and minorities and children: PDF attachment/ No Page limit	
		<ul style="list-style-type: none"> • This information must be the same as on the DCC application submitted under FOA PAR-18-410. • Describe the planned distribution of subjects by sex/gender, race, and ethnicity. • Describe the rationale for selection of sex/gender, racial, and ethnic group members in terms of the scientific objectives and proposed study design. The description may include, but is not limited to, information on the population characteristics of the disease or condition under study. • Describe proposed outreach programs for recruiting sex/gender, racial, and ethnic group members. • Inclusion and Excluded Groups: Provide a reason for limiting inclusion of any group by sex/gender, race, and/or ethnicity. In general, the cost of recruiting certain groups and/or geographic location alone are not acceptable reasons for exclusion of groups. • Existing datasets are resources: if existing datasets, resources or samples from other studies are used, address their inclusion <p>For NIH phase III clinical trials:</p> <ul style="list-style-type: none"> • It is mandatory to address plans for how sex/gender, race and ethnicity will be taken into consideration in the design and valid analysis of the trial <p>Valid analysis:</p>	

		<ul style="list-style-type: none"> • Inclusive eligibility criteria: cost of recruiting certain groups or geographic location alone are not acceptable to exclude a group. • Allocation of study participants of both sexes and from different racial and ethnic backgrounds to the study arms by an unbiased process such as randomization. • Unbiased evaluation of the outcomes of study participants. • Use of unbiased statistical analysis and proper methods of inference to estimate and compare intervention effects by sex/gender, race and or ethnicity, particularly if prior evidence strongly suggests that differences exist. • Plans to tests for differences if effect among sex/gender, racial and ethnic groups through discussion of one of the following: <ul style="list-style-type: none"> a. Address whether analysis will be done to detect significant differences in intervention effect along sex, race and ethnicity when prior studies strongly suggest there are significant differences amongst subgroups OR b. Plans to include and analyze sex/gender, racial, and/or ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups. (Representation of sex/gender, racial, and ethnic groups is not required as subject selection criteria, but inclusion is encouraged.), or c. Plans to conduct valid analyses of the intervention effect in sex/gender, racial, and/or ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect among subgroups. 	
15		Recruitment and Retention Plan: PDF attachment/No page limit	
		<ul style="list-style-type: none"> • Expertise of individuals responsible for screening, approaching and consenting potential pts. • Engagement of pt advocacy groups. • Process for identification and screening of study participants. • Primary and back-up recruitment strategies (use of EHR etc). 	

		<ul style="list-style-type: none"> • Implementation of consent processes. • Participant adherence and retention strategies. • Safeguards for vulnerable population if applicable. • Possible competing trials for participants. • Engagement of communities that will play a critical role in recruitment and retention. • Recruitment of groups for cluster-randomized trials. Provide a table of recruiting sites with site PI, showing enrollment goals and number of potential participants available for each site. 	
16.		Study Timeline: PDF attachment/No page limit	
		<p>Provide a <u>both</u> description and table/graph of the overall study timeline and key milestones</p> <ul style="list-style-type: none"> • Overall study timeline: include estimated time of study duration (in months) including when study opens to enrollment and final transfer of data to DCC will occur. Describe key milestones that need to be met throughout the trial (UG3 and UH3 phases), timetable of when these milestones will be met. • Aim of the CCC milestone plan is to describe those that need to be met by the CCC in coordination with activities of the DCC. • Key milestones: include relevant, measurable, results-focused and time-bound milestones for overall recruitment, enrollment and retention goals. Address milestones accrual goals for women, minorities and children and any other requirements for completion of approved research. • Include milestones for UG3 phase that should be met to successfully transition to the UH3 phase. Overall enrollment and site participation expected by the end of the UG3 phase will be agreed upon by the PI and NHLBI prior to award. Generally- one participant must be enrolled and 25% of sites activated at the end of UG3 phase. Describe milestones in UH3 phase to address specific aims and ensure successful completion of trial and dissemination of results. • Important milestones for CCC include: <ul style="list-style-type: none"> • Complete finalized protocol • Finalized ICF • Contracts/third party agreements 	

		<ul style="list-style-type: none"> • Training of sites • Final management/communication plan • Final data and safety monitoring plan • Site performance plan • Data completeness and quality monitoring reporting plan • Completion of regulatory approvals • 25% of sites activated • Enrollment of first subject in UG3 phase • UG3-UH3 transition meeting • Enrollment of 25%, 50%, 75% and 100% of projected recruitment, including women and minorities • Assessment of sites protocol implementation performance • Collection of data related to primary and secondary endpoints and database lock • Submission of primary manuscript to peer-reviewed scientific journals and dissemination of results • Submission of study results to clinicaltrials.gov within 12 months of primary completion date <p>NHLBI will conduct at least 2 admin reviews to determine progress: one at end of UG3 phase and the second within 2 years of the UH3 phase. The first may result in the revision of the milestones during the UG3/UH3 transition phase.</p>	
17		<p>Protection of human subjects: PDF attachment/No page limit</p>	
		<p>Section A: Risks to human subjects</p> <p><i>A(i) Human subject's involvement, characteristics and design:</i></p> <p>Briefly describe the overall study design.</p> <p>Describe the subject population(s) to be included in the study; the procedures for assignment to a study group, if relevant; and the anticipated numbers of subjects for each study group.</p> <p>List any collaborating sites where human subjects research will be performed, and describe the role of</p>	

those sites and collaborating investigators in performing the proposed research

A(ii) Study Procedures, Materials, and Potential Risks

Describe all planned research procedures (interventions and interactions) involving study subjects; how research material, including biospecimens, data, and/or records, will be obtained; and whether any private identifiable information will be collected in the proposed research project.

For studies that will include the use of previously collected biospecimens, data or records, describe the source of these materials, whether these can be linked with living individuals, and who will be able to link the materials.

Describe all the potential risks to subjects associated with each study intervention, procedure or interaction, including physical, psychological, social, cultural, financial, and legal risks; risks to privacy and/or confidentiality; or other risks. Discuss the risk level and the likely impact to subjects.

Where appropriate, describe alternative treatments and procedures, including their risks and potential benefits. When alternative treatments or procedures are possible, make the rationale for the proposed approach clear.

Section B Adequacy of Protection Against Risks

B(i). Informed Consent and Assent

Describe the process for obtaining informed consent. Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. When appropriate, describe how potential adult subjects' capacity to consent will be determined and the plans for obtaining consent from a legally authorized representative for adult subjects not able to consent.

If a waiver of some or all of the elements of informed consent will be sought, provide justification for the

waiver. Do not submit informed consent document(s) with your application unless you are requested to do so

B(ii) Protections Against Risk

Describe planned strategies for protecting against or minimizing all potential risks identified, including strategies to manage and protect the privacy of participants and confidentiality of research data.

Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects on participants.

Describe plans for handling incidental findings, such as those from research imaging, screening tests, or paternity tests.

B(iii). Vulnerable Subjects, if relevant to your study

Explain the rationale for the involvement of special vulnerable populations, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations.

Section C: Potential Benefits of the proposed Research to Research Participants and others

Discuss the potential benefits of the research to research participants and others.

Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to research participants and others.

Note: Financial compensation of subjects should not be presented as a benefit of participation in research.

Section D: Importance of the Knowledge to be Gained

Discuss the importance of the knowledge to be gained as a result of the proposed research.

		Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.	
18		Single IRB Plan: PDF attachment/no page limit	
		<ul style="list-style-type: none"> • Describe the single IRB Plan (should be same as DCC application). • Describe how you will comply with the NIH Policy on the Use of sIRB for Multi-Site Research. • Provide the name of the IRB that will serve as the sIRB of record. • Indicate that all identified participating sites have agreed to rely on the proposed sIRB and that any sites added after award will rely on the sIRB. • Briefly describe how communication between sites and the sIRB will be handled. • Indicate that all participating sites will, prior to initiating the study, sign an authorization/reliance agreement that will clarify the roles and responsibilities of the sIRB and participating sites. • Indicate which institution or entity will maintain records of the authorization/reliance agreements and of the communication plan. <p>Note: Do not include the authorization/reliance agreement(s) or the communication plan(s) documents in your application.</p> <p>For Studies with Legal, Regulatory, or Policy-based Claims for Exception as described by the sIRB Policy: Indicate that review by a sIRB will not be possible for all or some sites (specify which sites) because local IRB review is required by an existing federal/state/tribal law or policy. Include a specific citation to the relevant law, policy, or regulation.</p> <p>For sites requesting an exception based on compelling justification: Indicate which site(s) is requesting an exception to the use of the sIRB and provide compelling justification based on ethical or human subjects' protection issues or other well-justified reasons. NIH will determine whether to grant an</p>	

		exception following an assessment of the need. Note: If you intend to request an exception to the sIRB policy based on compelling justification, do not account for this exception in your proposed budget. The proposed budget must reflect any necessary sIRB costs without an exception (i.e., applicants should not assume that an exception will be granted when considering what sIRB costs to include in the budget).	
19		Data and safety monitoring plan: PDF attachment/no page limit	
		<p>This section should be the same as provided in the DCC application.</p> <ul style="list-style-type: none"> • Specify criteria for adverse event reporting, intervention discontinuation and stopping guidelines • For any proposed clinical trial, NIH requires a data and safety monitoring plan (DSMP) that is commensurate with the risks of the trial, its size, and its complexity. Provide a description of the DSMP, including: <ul style="list-style-type: none"> • The overall framework for safety monitoring and what information will be monitored. • The frequency of monitoring, including any plans for interim analysis and stopping rules (if applicable). • The process by which Adverse Events (AEs), including Serious Adverse Events (SAEs) such as deaths, hospitalizations, and life threatening events and Unanticipated Problems (UPs), will be managed and reported, as required, to the IRB, the person or group responsible for monitoring, the awarding IC, the NIH Office of Biotechnology Activities, and the Food and Drug Administration. • The individual(s) or group that will be responsible for trial monitoring and advising the appointing entity. Because the DSMP will depend on potential risks, complexity, and the nature of the trial, a number of options for monitoring are possible. These include, but are not limited to, monitoring by a: <ul style="list-style-type: none"> • PD/PI: While the PD/PI must ensure that the trial is conducted according to the approved protocol, in some cases (e.g., low risk trials, not blinded), 	

		<p>it may be acceptable for the PD/PI to also be responsible for carrying out the DSMP. o</p> <ul style="list-style-type: none"> • Independent safety monitor/designated medical monitor: a physician or other expert who is independent of the study. • Independent Monitoring Committee or Safety Monitoring Committee: a small group of independent experts. • Data and Safety Monitoring Board (DSMB): a formal independent board of experts including investigators and biostatisticians. NIH requires the establishment of DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally, for all Phase III clinical trials, although Phase I and Phase II clinical trials may also need DSMBs. If a DSMB is used, please describe the general composition of the Board without naming specific individuals. 	
20		Structure of the project team: PDF attachment/no page limit	
		<ul style="list-style-type: none"> • Include role of executive committee and steering committee and any internal or external advisory committee • Describe the oversight, responsibilities and coordination of sites or cores proposed • Describe role of any sub-investigators or providers, services, personnel or facilities. • Describe how these functions will integrate with the organizational framework with the DCC. • How DCC and CCC will coordinate leadership of clinical trial implementation and communications • Coordination with the separate components including NHLBI • Key channels used to reach and inform each stakeholder group and receive feedback. • Dispute resolution between CCC, DCC and all stakeholders 	
21		Statistical design and power: PDF attachment/no page limit	

		<ul style="list-style-type: none"> • Include a brief statement indicating that the CCC has worked closely with the DCC to ensure the number of expected subjects, expected effect size, power and statistical methods (for each outcome measure) have been adequately addressed. • State that the statistical design and power attachment is being submitted entirely as part of the collaborating DCC application. • Specify the number of subjects you expect to enroll, the expected effect size, the power, and the statistical methods you will use with respect to each outcome measures. • You will need to show that your methods for sample size and data analysis are appropriate given your plans for assignment of participants and delivery of interventions. For trials that randomize groups or deliver interventions to groups, special methods are required; additional information is available at the Research Methods Resources webpage 	
22		Dissemination Plan :PDF attachment/ no attachment	
		<p>This must be the same as described in the DCC application</p> <p>Explain briefly your plan for the dissemination of NIH-funded clinical trial information and address how the expectations of the policy will be met. The plan must contain sufficient information to assure the following:</p> <ul style="list-style-type: none"> • The applicant will ensure that clinical trial(s) under the award are registered and results information is submitted to ClinicalTrials.gov as outlined in the policy and per the specific timelines stated in the policy; • Informed consent documents for the clinical trial(s) will include a specific statement relating to posting of clinical trial information at ClinicalTrials.gov • The recipient institution has an internal policy in place to ensure that clinical trials registration and results reporting occur in compliance with policy requirements 	

23	<input type="checkbox"/>	Budgets – Modular or non-modular	
		Non-Modular/detailed – requesting more than \$250,000 per year in direct costs.	
		<ul style="list-style-type: none"> Proposals that seek more than \$500,000 in direct costs per year must be granted special permission from NIH. The current NIH salary cap is \$189,600 Each application in the cluster must include only its own budget, including any associated sub-awards Separate itemized budgets for each subcontract Budget justification to include details needs for each year Cores must be subcontracts to either CCC or DCC Include budget support for personnel to travel to DC for a yearly in person Steering Committee or investigator meeting/ NHLBI staff meetings Include budget support for publication and dissemination of results. DO NOT include budget for DSMB in CCC. This should be included in the DCC budget only. 	
25	<input type="checkbox"/>	Budget Justifications: PDF attachment/ no page limit	
		<p>Personnel Justification (applicable only to modular budgets)</p> <ul style="list-style-type: none"> List all personnel including names, number of person months (not % effort) devoted to the project (indicate academic, calendar, and/or summer) and roles on the project. Do not provide individual salary information. <p>Budget Justification (applicable to modular and non-modular budgets)</p> <p>http://grants.nih.gov/grants/policy/person_months_faqs.htm.</p> <ul style="list-style-type: none"> A detailed cost breakdown by cost category. All costs requested and all changes in the budget after year 1 should be clearly identified and justified. 	

Project title

PRINCIPAL PROPONENT NAME & APPLICANT
INSTITUTION

MEETING DATE

Meeting Agenda

Topics to be covered at staff consultation

NHLBI FOA title and agency division

Project Executive Committee

List members of project Executive Committee

Background of the project

Include pilot data and limitations of current data

Project Specific aims

Clearly list the specific aims and endpoints of the project (primary, secondary, exploratory etc.)

Project highlights

Research plan

- Project duration
- Sample size
- Sites included (Regions and number of sites)
- Overall budget

Study Design

- Randomized, double-blind, placebo controlled etc.
- Number of participants overall
- Breakdown of sites by participating region
- Study duration

Project details

- Flow of study participants within clinical trial (screening to last study visit)

Study inclusion/exclusion criteria

List Inclusion and Exclusion criteria as bullet points.

Biostatistical considerations

Sample size, justification of trial design

Analysis plan (interim and final)

Stopping criteria

Project delivery methods

- Project management expertise and tools
- Study organization and collaborators
- DSMB
- Communication between stakeholders
- Communication with NHLBI

Budget

- Overall study budget
- Breakdown of budget for each year of project
- Justification of budget

Public Health Impact

- Anticipated outcome
- Plans to disseminate study results with clinicians and the public
- Data sharing plan

Open discussion

Appendix III. Cover Letter template

On applicant institutional letter head

PI's name, designation and contact information

NHLBI Division Director's name

Director, Division of Cardiovascular Sciences (DCVS)

National Heart, Lung, and Blood Institute (NHLBI)

Bethesda, MD

Date

Dear (**NHLBI Division Director**)

I am including our submission titled "**1/N Project Title**" for consideration under the FOA: (PAR18-407), "Clinical Coordinating Center for Multi-Site Investigator-Initiated Clinical Trials (Collaborative UG3/UH3 Clinical Trial Required)". The applicant institution is (**Name of applicant institution**). The budget for year one in direct costs is \$ (**year 1 direct costs approved by NHLBI**) and for the overall study (**X years**) is \$ (**total direct costs of project approved by NHLBI**)

This submission is part of a cluster that contains XXX applications and they are:

1. Project 1/2 Clinical Coordinating Center (CCC) application:

Principal Investigator: Include PI name, designation and university information

2. Project 2/2 Data Coordinating Center (DCC) application:

Principal Investigator: Include PI name, designation and university information

No human or non-human genomic data will be generated in the proposed trial. There are no sub-award budgets that are not active in all periods.

Since the requested budget of the proposed grant in each period exceeds \$500,000 in direct costs a copy of the NHLBI acceptance letter to review this proposal is included.

I thank you for considering our request for support.

Sincerely,

PI name and signature

Appendix IV. NIH Biographical sketch for Key personnel

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Johns Doe, MD

eRA COMMONS USER NAME (credential, e.g., agency login): JDOE

POSITION TITLE: Director, Center for Coronary Interventions, and Professor of Medicine XXX University

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University XXX, New Jersey	M.D.	MM/YYYY	Medicine (4-yr program)
University XXX, Dallas, Tx	Residency	MM/YYYY	Internal Medicine
University XXX, Dallas, Tx	Fellowship	MM/YYYY	Cardiovascular Diseases
University XXX, Dallas, Tx	Fellowship	MM/YYYY	Interventional Cardiology

A. Personal Statement

On the proposed application “Project Title”, I will function as the project PI. My experience includes serving as a Principal Investigator on several multi-site clinical trials since 2008 specializing in the field of coronary intervention. I recently completed a multi-site randomized, controlled, double-blinded clinical trial in (project area) funded by the NIH through the R01 mechanism to study (include project objective). I have also served as the PI of data coordinating centers that create, manage, and control data quality in the area of (project area) over the last XXX years. As a PI of these studies, I have overseen data management and development of case report forms, patient safety, risk management, project management and statistical methods. I have served as a member of Data and

Safety Monitoring Boards (DSMB), both on industry sponsored and NIH trials. I have also been a member of study Executive Committees. I have over 18 years' experience in coordinating, building and managing patient registry databases. The XXX (project title) trial in keeping with the philosophy to promote research and equipped with the experience of the study leadership will provide evidence-based knowledge to the medical community regarding a largely unanswered question on XXX (project objective)

B. Positions and Honors

List major positions and honors in this section by year.

Other Experience and Professional Memberships

List important professional memberships here

C. Contributions to Science

List 5 of the most current contributions to science here. For each contribution, list up to 4 related publications. Contribution can include trials conducted and their outcomes, publications such as books etc.

Complete List of Published Work: Insert link to complete bibliography of publications obtained from NIH MyBibliography page

D. Additional Information: Research Support and/or Scholastic Performance

List ongoing research here in the format noted below.

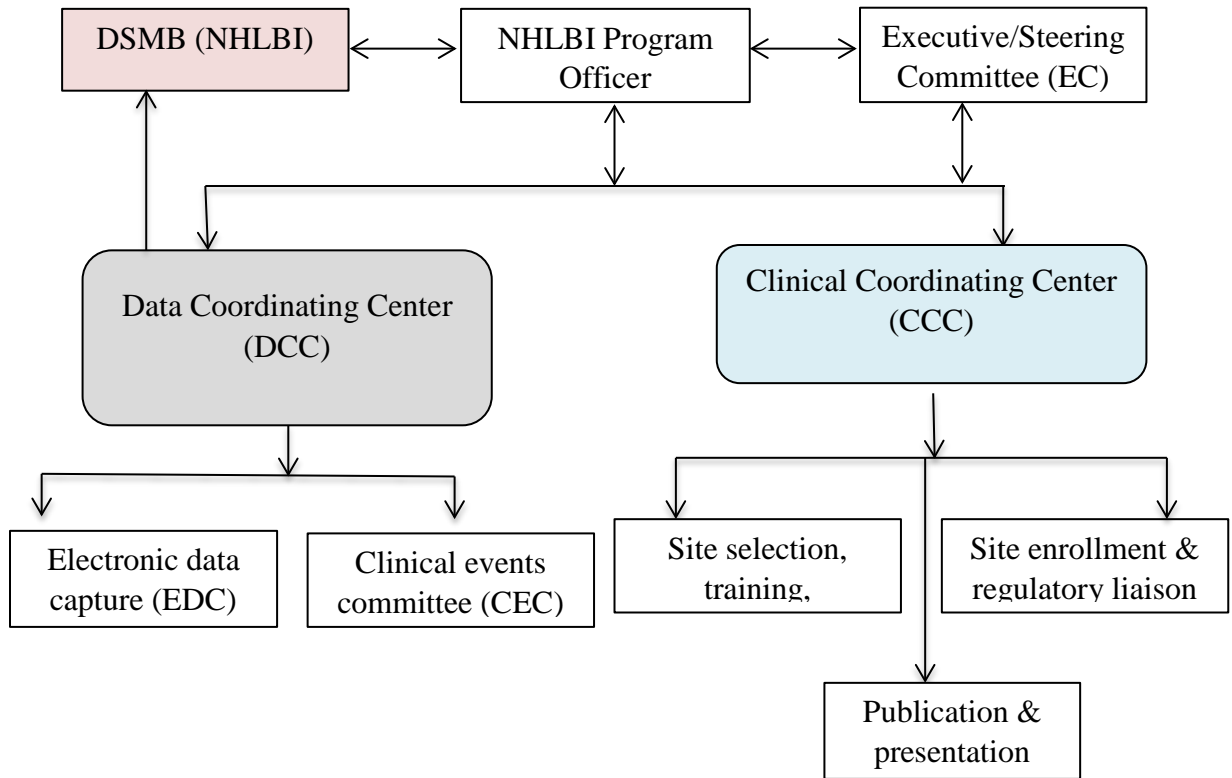
Sponsor name project	Role in Project	Dates of
-------------------------	-----------------	----------

Title of project

Sponsor name project	Role in Project	Dates of
-------------------------	-----------------	----------

Title of project

Appendix V. Structure of Project Team



Study executive committee (EC): List names of personnel

CCC: Name of Institution

DCC: Name of Institution

Appendix VI. Site survey

Study Title:

Brief introduction to the study and purpose of survey

Site Information	
Site name and address	
Site PI Name:	
Site PI Specialty:	
Site PI e-mail address	
Site PI phone number	
Sub-Investigator name (if applicable)	
Sub-Investigator Specialty	

Participation Metrics	
Name and address of hospital where study will be conducted	
Are you interested in participating in XXX Trial?	<input type="radio"/> Yes <input type="radio"/> No
On an average, how many patients per month with (insert main inclusion criteria here) at your hospital	_____ patients per month
Of the numbers of patients per month noted above, how many patients would be eligible for this trial based on the inclusion/exclusion criteria provided	

IRB/Ethics Committee information	
Is your site able to use a Central IRB (CIRB)	<input type="radio"/> Yes <input type="radio"/> No
If yes, select all CIRB reviews acceptable	<input type="radio"/> Copernicus IRB <input type="radio"/> Western IRB <input type="radio"/> Schulman IRB

	<input type="radio"/> Other(specify)_____
Does your local IRB/site have a reliance agreement with a CIRB	<input type="radio"/> Yes: Specify_____
Does you site need approval form othet local committees (R&D committee, pre-review committee)	<input type="radio"/> No

Facilities and Resources	
Do you have dedicated office space to conduct research?	<input type="radio"/> Yes
Do you have adequate space with limited access to control research materials (lab kits, study charts)	<input type="radio"/> No
Does your site have research coordinators that can be assigned to this trial?	<input type="radio"/> Yes
Does you site have access to a compute to randomize patients and enter study data?	<input type="radio"/> No
Does you site use Electronic Medical Records (EMR)?	<input type="radio"/> Yes
Does your site have a dedicated research pharmacy to store and dispense study medication?	<input type="radio"/> No
If no, please describe where study medication will be stored/dispensed?	

Appendix VII. Letter of Support from Participating Site

Please insert organization's letterhead)

Enter Project PI name and institution

Date

Re: Enter project title

Dear Dr. XXXX,

I am pleased to state my interest in participating as the Site Principal Investigator in the XXX Trial (insert project title), involving ...state study objective.

Our hospital is commonly faced with this clinical question involving the care of cardiovascular patients with this condition and as the Principal Investigator at _____, (insert site name) I would like to participate in this first randomized clinical that would benefit patients and providers alike. We have the necessary patient population to approach and can enroll ____ patients per month into this study. We are willing to collaborate with providers across specialties to build a referral base.

Sincerely,

Site PI name and signature

Appendix VIII. Study timelines template

UG3 Phase	
Study process	Timeline (MMM/YYYY)
Study protocol, ICF, case report forms. Form study management groups. Finalize SOP and process documents for each group	Jan-Mar YYYY
Project personnel and site training plan and manual	Mar-Apr YYYY
Primary and back-up site selections	Feb-Apr YYYY
EDC set-up	Apr-May YYYY
Site Contracting	Apr- Jun YYYY
Central IRB contracting and submissions. Approval of first 5 sites.	Apr-Jun YYY
DSMB, CEC, other committees (formation/charter), regional hubs	Jun-Jul YYYY
Site training/initiation (25% of total planned)	Jul-Oct YYYY
First patient enrolled	Nov-Dec YYY

NHLBI review of UG3 accomplishments and approval to transition to UH3 phase: Dec
YYYY

UH3 Phase	
Study process	Timeline (MMM/YYYY)
Activation of remaining sites	Jan –Mar YYYY (year 2)
Enrollment of up to 200 patients	Jan-Dec YYYY (year 2)
Enrollment of patients 201-500	Jan-Dec YYYY (year 3)
Enrollment of patients 501-800 (Interim analysis at Pt #658)	Jan-Dec YYYY (year 4)
Enrollment of patients 801-1000	Jan-Sep YYYY (year 5)
Last Patient Last visit	Oct YYYY (Year 5)
Data clean up, and database lock	Jun-Dec YYYY (Year 5)
Statistical analysis	Nov-Dec YYYY (Year 5)
Publication/Presentation and Data submission to NHLBI central repository	Jan- Mar YYYY (Year 6)

Appendix IX. Budget template

Budget template for year 1 of funding is included here. This template can be duplicated to create the budget for subsequent years of funding

Jan YYYY-Dec YYYY							
	Unit	hours	cost/unit or rate/hr or /year	base salary	30% fringe	Line item cost	Comments
					X Base		
Project start up costs							
Site start up costs	12		2,000			24000	NIH expects 25% of sites are activated at end of 1 year/UG3 phase(25% of 50 sites=12 sites). Budgeted here for 25 sites to be activated
IRB costs						60,000	Central IRB charges for 25 sites=\$60,000
Site reimbursement cost /pt	100		2000			200000	UG3 phase requires 1 pt to be enrolled. Budgeted here for 100 patients in year 1
Personnel salaries							
CCC Management							
Principal Investigator	1		121,550	93500	28050	121,550	6 calendar months (0.5X 187,000+30% fringe). NHLBI salary cap \$187,000
Consultant	1	50	250			12,500	50 hours @\$250/hr
Project Manager	1			60000	18000	78,000	1 FTE
Administrative staff	2			30,000.00	9,000.00	78,000	Base salary= 30,000, fringe at 30% . In year 1, project needs 2 admin staff at 1 FTE each
Other costs							

Study materials						4200	Study binders (\$8 per piece/ 100 binders) =800 office supplies: \$2000 patient cards= 1000 cards at \$1 per card=1000 study posters= 100 posters @ \$4 per poster= \$400
Study website	1					10,000	project
Study travel (NIH+ sites)	10		3,150			31500	mileage and airfare between Dallas and
Study meetings	1		50,000			50000	beginning of year 2
DCC	5		2,500			12500	meetings
Total year 1						\$682,250	
budget						\$683,000	

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Appendix 2. Biography

Preeti P Kamath is currently a Clinical Team Manager with a large CRO and oversees clinical trials in North America. Prior to her current role, she was the Clinical Research Manager at a premier medical university and academic center in Dallas, Texas. She served as the Project Manager on several clinical trials funded by pharmaceutical/device companies and Federal agencies such as the Veterans Health Administration and National Institutes of Health. She has also held the role of research coordinator and IRB Administrator in her career spanning 12 years in the field of research. She is a dentist by training and received her Bachelor's in Dental Surgery degree from Bangalore, India and Master's in Healthcare Administration from University of Texas, Arlington prior to completing her Master of Science in Research Administration at Johns Hopkins University.